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USPT	Diabetes	10627	L1

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#5990077
#5981488
#5977071

L9 ANSWER 1 OF 3 MEDLINE
AN 2000036953 MEDLINE
DN 20036953
TI Present and potential future use of **gene therapy** for the treatment of non-insulin dependent **diabetes** mellitus (Review).
AU Freeman D J; Leclerc I; Rutter G A
CS Department of Biochemistry, School of Medical Sciences, University Walk, University of Bristol, Bristol BS8 1TD, UK.
SO Int J Mol Med, (1999 Dec) 4 (6) 585-92. Ref: 62
Journal code: C8H. ISSN: 1107-3756.
CY Greece
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, ACADEMIC)
LA English
FS Priority Journals
EM 200003
EW 20000303
AB This review describes the latest approaches towards using **gene therapy** as a treatment for non-insulin dependent **diabetes** mellitus (NIDDM; Type 2 **diabetes**). We examine attempts to directly deliver the insulin gene to non-beta-cells, to improve insulin secretion from existing beta-cells and to develop ex vivo approaches to implanting genetically modified cells. Future research into the pathology of non-insulin dependent **diabetes**, combined with the latest developments in gene delivery systems, may potentially make **gene therapy** an attractive alternative NIDDM treatment in the future.
CT Check Tags: Animal; Human; Support, Non-U.S. Gov't
Adult
Blood Glucose: AN, analysis
Cell Transplantation
Diabetes Mellitus, Non-Insulin-Dependent: GE, genetics
Diabetes Mellitus, Non-Insulin-Dependent: PP, physiopathology
***Diabetes Mellitus, Non-Insulin-Dependent: TH, therapy**
Gene Expression Regulation
***Gene Therapy**
Genes, Synthetic
Genetic Vectors
Glucagon: GE, genetics
Glucagon: PH, physiology
Glucokinase: GE, genetics
Glucokinase: PH, physiology
Hyperinsulinism: ET, etiology
Hypoglycemic Agents: PD, pharmacology
Hypoglycemic Agents: TU, therapeutic use
*Insulin: GE, genetics
Insulin: SE, secretion
Insulin Resistance
Islets of Langerhans: DE, drug effects
Islets of Langerhans: SE, secretion
Islets of Langerhans Transplantation
Mice
Middle Age
Monosaccharide Transport Proteins: GE, genetics
Monosaccharide Transport Proteins: PH, physiology
Muscle Contraction
Nitric Oxide: PH, physiology
Nitric-Oxide Synthase: GE, genetics
Nitric-Oxide Synthase: PH, physiology

Peptide Fragments: GE, genetics
Peptide Fragments: PH, physiology
Promoter Regions (Genetics)
Protein Precursors: GE, genetics
Protein Precursors: PH, physiology
Proteins: GE, genetics
Proteins: PH, physiology
Rats
Trans-Activators: GE, genetics
Trans-Activators: PH, physiology
RN 10102-43-9 (Nitric Oxide); 11061-68-0 (Insulin); **89750-14-1 (glucagon-like peptide 1); 9007-92-5 (Glucagon)**
CN EC 1.14.13.- (neural constitutive nitric oxide synthase); EC 1.14.13.39 (Nitric-Oxide Synthase); EC 2.7.1.2 (Glucokinase); 0 (insulin promoter factor 1); 0 (islet neogenesis-associated protein); 0 (Blood Glucose); 0 (Genetic Vectors); 0 (GLUT-2 protein); 0 (Hypoglycemic Agents); 0 (Monosaccharide Transport Proteins); 0 (Peptide Fragments); 0 (Protein Precursors); 0 (Proteins); 0 (Trans-Activators)

L9 ANSWER 2 OF 3 MEDLINE
AN 1999459160 MEDLINE
DN 99459160
TI Glucose regulation of the expression of the **glucagon** receptor gene.
AU Svoboda M; Portois L; Malaisse W J
CS Laboratory of Biochemistry and Nutrition, Universite Libre de Bruxelles, Brussels, B-1070, Belgium.. msvobod@.ulb.ac.be
SO MOLECULAR GENETICS AND METABOLISM, (1999 Oct) 68 (2) 258-67. Ref: 86
Journal code: CXY. ISSN: 1096-7192.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA English
FS Priority Journals
EM 200004
EW 20000402
AB The **glucagon** receptor gene is a member of a gene family, the expression of which is strongly upregulated by glucose. This review deals with the structure of both the **glucagon** receptor gene and its promoter. Attention is focused on the glucose regulatory element that we discovered in the promoter of this gene. Regulation by glucose of genes implicated in glucose homeostasis represents one mechanism contributing to the control of fuel utilization. Its deficiency or imbalance could potentially lead to or participate in pathological situations such as **diabetes** mellitus. On the other hand, the regulatory element of the **glucagon** receptor gene promoter could be used as a tool for the glucose-regulated expression of other genes. Indeed, an analysis of the **glucagon** receptor gene promoter demonstrated that only a short fragment of the genomic DNA, easy to subclone, contains all required elements for activation by glucose. Its potential use for **gene therapy** is also considered, therefore, in this report. Copyright 1999 Academic Press.
CT Check Tags: Animal; Human; Support, Non-U.S. Gov't
Amino Acid Sequence
Dose-Response Relationship, Drug
Gene Expression Regulation: DE, drug effects
*Glucose: PD, pharmacology
Molecular Sequence Data
Promoter Regions (Genetics)
***Receptors, Glucagon: GE, genetics**
Sequence Homology, Amino Acid
RN 50-99-7 (Glucose)
CN 0 (Receptors, **Glucagon**)

L9 ANSWER 3 OF 3 MEDLINE
AN 95241489 MEDLINE
DN 95241489
TI **Gene therapy** for **diabetes** mellitus in rats by hepatic expression of insulin.
AU Kolodka T M; Finegold M; Moss L; Woo S L
CS Howard Hughes Medical Institute, Baylor College of Medicine, Houston, TX 77030, USA..
SO PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, (1995 Apr 11) 92 (8) 3293-7.
Journal code: PV3. ISSN: 0027-8424.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 199507
AB Type 1 **diabetes** mellitus is caused by severe insulin deficiency secondary to the autoimmune destruction of pancreatic beta cells. Patients need to be controlled by periodic insulin injections to prevent the development of ketoacidosis, which can be fatal. Sustained, low-level expression of the rat insulin 1 gene from the liver of severely diabetic rats was achieved by in vivo administration of a recombinant retroviral vector. Ketoacidosis was prevented and the treated animals exhibited normoglycemia during a 24-hr fast, with no evidence of hypoglycemia. Histopathological examination of the liver in the treated animals showed no apparent abnormalities. Thus, the liver is an excellent target organ for ectopic expression of the insulin gene as a potential treatment modality for type 1 **diabetes** mellitus by **gene therapy**.
CT Check Tags: Animal; Male; Support, Non-U.S. Gov't
Base Sequence
Blood Glucose: AN, analysis
C-Peptide: BL, blood
***Diabetes Mellitus, Experimental: TH, therapy**
Gene Expression
***Gene Therapy: MT, methods**
Genetic Vectors
Glucagon: BL, blood
Insulin: BL, blood
Insulin: GE, genetics
Insulin: ME, metabolism
*Insulin: TU, therapeutic use
Ketones: BL, blood
Liver: AH, anatomy & histology
*Liver: ME, metabolism
Molecular Sequence Data
Rats
Recombinant Proteins: TU, therapeutic use
Retroviridae: GE, genetics
Streptozocin
Survival Analysis
Transduction, Genetic
RN 11061-68-0 (Insulin); 18883-66-4 (Streptozocin); **9007-92-5 (Glucagon)**
CN 0 (Blood Glucose); 0 (C-Peptide); 0 (Genetic Vectors); 0 (Ketones); 0 (Recombinant Proteins)

12/7

L5 ANSWER 1 OF 126 CAPLUS COPYRIGHT 1999 ACS
AN 1999:767688 CAPLUS
TI **Glucagon-like peptide 2** decreases mortality and reduces the severity of indomethacin-induced murine enteritis
AU Boushey, Robin P.; Yusta, Bernardo; Drucker, Daniel J.
CS Department of Medicine, Banting and Best Diabetes Centre, The Toronto General Hospital, University of Toronto, Toronto, ON, M5G2C4, Can.
SO Am. J. Physiol. (1999), 277(5, Pt. 1), E937-E947
CODEN: AJPHAP; ISSN: 0002-9513
PB American Physiological Society
DT Journal
LA English
CC 2 (Mammalian Hormones)
AB Glucagon-like peptides (GLPs) are secreted from enteroendocrine cells in the gastrointestinal tract. **GLP-1** actions regulate blood glucose, whereas GLP-2 exerts trophic effects on intestinal mucosal epithelium. Although **GLP-1** actions are preserved in diseases such as **diabetes**, GLP-2 action has not been extensively studied in the setting of intestinal disease. We have now evaluated the biol. effects of a human GLP-2 analog in the setting of exptl. murine nonsteroidal antiinflammatory drug-induced enteritis. Human (h)[Gly2]GLP-2 significantly improved survival whether administered before, concomitant with, or after indomethacin. H[Gly2]GLP-2-treated mice exhibited reduced histol. evidence of disease activity, fewer intestinal ulcerations, and decreased myeloperoxidase activity in the small bowel ($P < 0.05$, h[Gly2]GLP-2- vs. saline-treated controls). H[Gly2]GLP-2 significantly reduced cytokine induction, bacteremia, and the percentage of pos. splenic and hepatic bacterial cultures ($P < 0.05$). H[Gly2]GLP-2 enhanced epithelial proliferation ($P < 0.05$ for increased crypt cell proliferation in h[Gly2]GLP-2- vs. saline-treated mice after indomethacin) and reduced apoptosis in the crypt compartment ($P < 0.02$). These observations demonstrate that a human GLP-2 analog exerts multiple complementary actions that serve to preserve the integrity of the mucosal epithelium in exptl. gastrointestinal injury in vivo.

L5 ANSWER 2 OF 126 CAPLUS COPYRIGHT 1999 ACS
AN 1999:707189 CAPLUS
TI **Glucagon-like peptide-1**, a gastrointestinal hormone with a pharmaceutical potential
AU Holst, Jens Juul
CS Department of Medical Physiology, the Panum institute, University of Copenhagen, Copenhagen, DK-2200, Den.
SO Curr. Med. Chem. (1999), 6(11), 1005-1017
CODEN: CMCHE7; ISSN: 0929-8673
PB Bentham Science Publishers
DT Journal
LA English
CC 2 (Mammalian Hormones)
AB **Glucagon-like peptide-1** (**GLP-1**) is an insulinotropic hormone secreted from endocrine cells in the gut mucosa in response to meal ingestion. It is an important incretin hormone; mice with a null mutation in the **GLP-1** receptor gene develop glucose intolerance. In addn., it inhibits gastrointestinal secretion and motility and is thought to be part of the "ileal brake" mechanism. Perhaps because of the latter actions it inhibits food intake, but intracerebral injection of **GLP-**

1 also inhibits food intake. The insulinotropic effect is preserved in patients with type 2 **diabetes** mellitus, in whom also glucagon secretion is inhibited. Thus upon iv **GLP-1** infusion blood glucose may be completely normalized. Because its actions are glucose-dependent hypoglycemia does not develop. However, **GLP-1** is metabolised extremely rapidly in vivo, initially by a mechanism that involves the enzyme dipeptidyl peptidase-IV. It is currently being investigated how **GLP-1** or analogs thereof can be employed in practical **diabetes** therapy. Promising solns. include the development of stable analogs and inhibitors of the degrading enzyme.

L5 ANSWER 3 OF 126 CAPLUS COPYRIGHT 1999 ACS
AN 1999:699517 CAPLUS
DN 131:318094
TI Inhibition of dipeptidyl peptidase IV with NVP-DPP728 increases plasma **GLP-1** (7-36 amide) concentrations and improves oral glucose tolerance in obese Zucker rats
AU Balkan, B.; Kwasnik, L.; Miserendino, R.; Holst, J. J.; Li, X.
CS Novartis Institute Biomedical Research, Summit, NJ, 07901, USA
SO Diabetologia (1999), 42(11), 1324-1331
CODEN: DBTGAJ; ISSN: 0012-186X
PB Springer-Verlag
DT Journal
LA English
CC 2-6 (Mammalian Hormones)
Section cross-reference(s): 14
AB The potent incretin hormone **glucagon-like peptide 1** (**GLP-1**) plays a pivotal role in prandial insulin secretion. In the circulation **GLP-1** (7-36) amide is, however, rapidly (t1/2: 1-2 min) inactivated by the protease dipeptidyl peptidase IV (DPP-IV). We therefore investigated whether DPP-IV inhibition is a feasible approach to improve glucose homeostasis in insulin resistant, glucose intolerant fatty Zucker rats, a model of mild Type II (non-insulin-dependent) **diabetes** mellitus. An oral glucose tolerance test was done in lean and obese male Zucker rats while plasma DPP-IV was inhibited by the specific and selective inhibitor NVP-DPP728 given orally. Inhibition of DPP-IV resulted in a significantly amplified early phase of the insulin response to an oral glucose load in obese falfa rats and restoration of glucose excursions to normal. In contrast, DPP-IV inhibition produced only minor effects in lean FA/ rats. Inactivation of **GLP-1** (7-36) amide was completely prevented by DPP-IV inhibition suggesting that the effects of this compd. on oral glucose tolerance are mediated by increased circulating concns. of **GLP-1** (7-36) amide. Reduced gastric emptying, as monitored by paracetamol appearance in the circulation after an oral bolus, did not appear to have contributed to the reduced glucose excursion. It is concluded that NVP-DPP728 inhibits DPP-IV and improves insulin secretion and glucose tolerance, probably through augmentation of the effects of endogenous **GLP-1**. The improvement obsd. in prandial glucose homeostasis during DPP-IV inhibition suggests that inhibition of this enzyme is a promising treatment for Type II **diabetes**.
ST NVPDPP728 dipeptidyl peptidase IV insulin gastric emptying
IT Gastric emptying
Obesity
(inhibition of dipeptidyl peptidase IV with NVP-DPP728 increases plasma **GLP-1** concns. and improves oral glucose tolerance in obese Zucker rats)
IT **Diabetes** mellitus

(non-insulin-dependent; inhibition of dipeptidyl peptidase IV with NVP-DPP728 increases plasma **GLP-1** concns. and improves oral glucose tolerance in obese Zucker rats)

IT 247016-69-9, NVP-DPP 728
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(inhibition of dipeptidyl peptidase IV with NVP-DPP728 increases plasma **GLP-1** concns. and improves oral glucose tolerance in obese Zucker rats)

IT 89750-14-1, Glucagon-like peptide I
RL: BOC (Biological occurrence); BIOL (Biological study); OCCU (Occurrence)
(inhibition of dipeptidyl peptidase IV with NVP-DPP728 increases plasma **GLP-1** concns. and improves oral glucose tolerance in obese Zucker rats)

IT 50-99-7, Glucose, biological studies 9004-10-8, Insulin, biological studies 54249-88-6, Dipeptidyl peptidase IV
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(inhibition of dipeptidyl peptidase IV with NVP-DPP728 increases plasma **GLP-1** concns. and improves oral glucose tolerance in obese Zucker rats)

L5 ANSWER 4 OF 126 CAPLUS COPYRIGHT 1999 ACS
AN 1999:691200 CAPLUS
DN 131:295928
TI Genetic engineering of neuroendocrine cells for glucose-dependent secretion of insulin
IN Powers, Alvin C.; Wu, Lan
PA Vanderbilt University, USA
SO PCT Int. Appl., 62 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM C12N015-00
ICS C12N015-63; C12N015-11; A61K035-00; A61K035-55; A61K035-30
CC 2-6 (Mammalian Hormones)
Section cross-reference(s): 3, 63
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 9954451	A1	19991028	WO 1999-US8628	19990420

W: AU, CA, JP
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE

PRAI US 1998-82366 19980420

AB The present invention provides an engineered cell comprising a gene encoding a non-glucose insulin secretagogue receptor and an insulin gene, wherein at least one of said genes is a recombinant gene and the cell secretes insulin in response to glucose wherein at least one of said genes has been introduced into the cell by means of a recombinant vector. Representative examples of non-glucose insulin secretagogue receptors include receptors for **glucagon-like peptide 1** (**GLP-1**), glucose-dependent insulin-releasing polypeptide, cholecystokinin, gastrin, secretin, and gastric inhibitory peptide. The cell is derived from a cell capable of forming secretory granules, such as a pituitary or thyroid or adrenal cell. Thus, pituitary cells infected with both a recombinant **GLP-1** receptor adenovirus and a recombinant insulin adenovirus secrete insulin at physiol. **GLP-1** levels. Recombinant adenovirus- or adeno-assocd. virus-mediated expression of glucokinase or glucokinase with

a glucose transporter (GLUT2 or GLUT3) endows neuroendocrine cells with glucose-regulated insulin secretion. These "artificial beta cells" that secrete insulin in response to glucose can be employed in the clin. treatment of insulin-dependent **diabetes** mellitus. Also provided is a method for producing insulin, comprising: (a) culturing the cell; (b) stimulating said cell to secrete insulin; and (c) collecting the secreted insulin.

ST neuroendocrine cell insulin secretion genetic engineering; beta cell artificial insulin secretion genetic engineering; receptor insulin secretagogue cloning neuroendocrine cell; gene therapy insulin secretion neuroendocrine cell

IT Virus vectors
(adenovirus; genetic engineering of neuroendocrine cells for glucose-dependent secretion of insulin)

IT .beta.-Cell
(artificial; genetic engineering of neuroendocrine cells for glucose-dependent secretion of insulin)

IT Gastrointestinal hormone receptors
Peptide receptors
RL: BUU (Biological use, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(gastric inhibitory polypeptide; genetic engineering of neuroendocrine cells for glucose-dependent secretion of insulin)

IT Adrenal medulla
Antidiabetic agents
Gene therapy
Genetic engineering
Neuroendocrine system
Pituitary gland
Protein secretion
Thyroid gland
(genetic engineering of neuroendocrine cells for glucose-dependent secretion of insulin)

IT CCK-B receptor
Cholecystokinin receptors
GLUT2 glucose transporter
GLUT3 glucose transporter
Glucagon-like peptide-1 receptors
Secretin receptors
RL: BUU (Biological use, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(genetic engineering of neuroendocrine cells for glucose-dependent secretion of insulin)

IT Protein receptors
RL: BUU (Biological use, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(insulin-releasing polypeptide; genetic engineering of neuroendocrine cells for glucose-dependent secretion of insulin)

IT Adeno-associated virus
Human adenovirus
(vectors; genetic engineering of neuroendocrine cells for glucose-dependent secretion of insulin)

IT 362-74-3, Dibutyryl cAMP 28822-58-4, Isobutyl methyl xanthine 66575-29-9, Forskolin
RL: BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)
(co-stimulator; genetic engineering of neuroendocrine cells for glucose-dependent secretion of insulin)

IT 50-99-7, Glucose, biological studies
RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)
(genetic engineering of neuroendocrine cells for glucose-dependent secretion of insulin)

IT 9004-10-8P, Insulin, biological studies 11061-68-0P, Human insulin
RL: BMF (Bioindustrial manufacture); MFM (Metabolic formation); THU

(Therapeutic use); BIOL (Biological study); FORM (Formation, nonpreparative); PREP (Preparation); USES (Uses)
(genetic engineering of neuroendocrine cells for glucose-dependent secretion of insulin)

IT 9001-36-9, Glucokinase
RL: BUU (Biological use, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(genetic engineering of neuroendocrine cells for glucose-dependent secretion of insulin)

IT 1393-25-5, Secretin 9002-76-0, Gastrin 9011-97-6, Cholecystokinin 54241-84-8, Insulin-releasing polypeptide 59392-49-3, Gastric inhibitory polypeptide 89750-14-1, Glucagon-like peptide I
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(receptor; genetic engineering of neuroendocrine cells for glucose-dependent secretion of insulin)

L5 ANSWER 5 OF 126 CAPLUS COPYRIGHT 1999 ACS
AN 1999:673040 CAPLUS
DN 131:327484
TI Methods of delivering **glucagon-like peptide-1-**(7-37) (**GLP-1**) and derivatives for treatment of human **diabetes** and obesity
IN Thorens, Bernard
PA Modex Therapeutiques S. A., Switz.
SO PCT Int. Appl., 33 pp.
CODEN: PIXXD2
DT Patent
LA English
IC C12N015-16; A61K038-26
CC 63-3 (Pharmaceuticals)
Section cross-reference(s): 3, 14

FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 9953064	A2	19991021	WO 1999-IB651	19990413

W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT
RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRAI US 1998-PV81562 19980413

AB Methods of delivering **glucagon-like peptide-1 GLP-1** or a **GLP-1** mutein, preferably the Gly8 mutein, for the treatment of Type II **diabetes** and obesity, are disclosed. Preferably, the **GLP-1** is delivered using encapsulated **GLP-1**-secreting cells.

ST cloning GLP1 secreting cell encapsulation delivery **diabetes** obesity therapy; semipermeable membrane encapsulation GLP1 secreting cell **diabetes** obesity therapy

IT Animal cell line
(**GLP-1** secreting; methods of delivering **glucagon-like peptide-1-**(7-37) (**GLP-1**) and derivs. for treatment of human **diabetes** and obesity)

IT Drug delivery systems
(implants; methods of delivering **glucagon-like peptide-1-**(7-37) (**GLP-1**) and derivs. for treatment of human **diabetes** and obesity)

IT Drug delivery systems
(injections; methods of delivering **glucagon-like peptide-1-**(7-37) (**GLP-1**) and derivs. for treatment of human **diabetes** and obesity)

IT Obesity
(methods of delivering **glucagon-like peptide-1**-(7-37) (**GLP-1**) and derivs. for treatment of human **diabetes** and obesity)
IT **Diabetes** mellitus
(non-insulin-dependent; methods of delivering **glucagon-like peptide-1**-(7-37) (**GLP-1**) and derivs. for treatment of human **diabetes** and obesity)
IT Encapsulation
(of implant; methods of delivering **glucagon-like peptide-1**-(7-37) (**GLP-1**) and derivs. for treatment of human **diabetes** and obesity)
IT Drug delivery systems
(oral; methods of delivering **glucagon-like peptide-1**-(7-37) (**GLP-1**) and derivs. for treatment of human **diabetes** and obesity)
IT Membranes, nonbiological
(semipermeable, implant encapsulation; methods of delivering **glucagon-like peptide-1**-(7-37) (**GLP-1**) and derivs. for treatment of human **diabetes** and obesity)
IT 247173-91-7 247174-37-4 247174-49-8 247174-57-8 247174-68-1
247174-74-9 247174-76-1 247174-78-3 247174-82-9
RL: PRP (Properties)
(Unclaimed; methods of delivering **glucagon-like peptide-1**-(7-37) (**GLP-1**) and derivs. for treatment of human **diabetes** and obesity)
IT 106612-94-6P 246048-14-6P 248596-39-6P
RL: BPN (Biosynthetic preparation); BPR (Biological process); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); PROC (Process); USES (Uses)
(methods of delivering **glucagon-like peptide-1**-(7-37) (**GLP-1**) and derivs. for treatment of human **diabetes** and obesity)

L5 ANSWER 6 OF 126 CAPLUS COPYRIGHT 1999 ACS
AN 1999:636574 CAPLUS
DN 131:252646
TI New developments in the treatment of type 1 **diabetes** mellitus
AU Haak, Thomas
CS Medical Dep. I, Center Internal Medicine, Diabetes-Schulungszentrum, Johann Wolfgang Goethe-Univ., Frankfurt/Main, D-60590, Germany
SO Exp. Clin. Endocrinol. Diabetes (1999), 107(Suppl. 3), S108-S113
CODEN: ECEDFQ; ISSN: 0947-7349
PB Johann Ambrosius Barth
DT Journal; General Review
LA English
CC 2-0 (Mammalian Hormones)
Section cross-reference(s): 63
AB A review with 38 refs. is given on the new developments in the treatment and management of type-1-**diabetes** mellitus. Treatment of type 1 **diabetes** mellitus has made tremendous advances within the last decades. With concern to insulin delivery there are 2 promising new approaches. One is the intrapulmonary insulin delivery which has become feasible by the development of new inhalation devices which provide a sufficient degree of intrapulmonary drug retention. Also oral insulin delivery seems feasible when surface active substances are used to cross the mucosal membrane in the gut. Clin. research has also focussed on coatings for the insulin mols. to solve the problem raised by the proteolytic activity of the digestive system. A very new agent produced by a fungus called Pseudomassaria was demonstrated to reverse the clin. signs of **diabetes** mellitus in mice. The compd. diffuses through the cell membrane, binds to the inner part of the insulin receptor and activates the insulin typical biol. effects. Nowadays a variety of insulin analogs are designed and tested for their clin. use. By shifting

the isoelec. point towards to a slightly acidic pH, HOE 901 ppts. at physiol. pH resulting in a const. and peakless insulin delivery. NN 304 is a 14-carbon aliph. fatty acid acylated analog that binds to serum albumin resulting in a flatter time-action profile than NPH insulin. Also rapid acting insulin analogs are or will be launched in the near future aiming to ensure an improved postprandial glucose regulation. **Glucagon-like peptide-1** (**GLP-1**) improves metabolic control by a variety of effects, e.g. the enhancement of insulin secretion and inhibition of glucagon secretion. **GLP-1** reduces food and water intake controlled by the brain, and inhibits gastric emptying. A disadvantage of **GLP-1** is its very short half-life. Novel derivs. with the beneficial effects of **GLP-1** but a better resistance against degrdn. were designed. In addn. substances were developed inhibiting **GLP-1** degrdn. or augmenting **GLP-1** release from its abundant endogenous pool. There is a variety of interesting approaches aiming to improve or ease blood glucose self-monitoring. One is the development of s.c. catheters for continuous blood glucose control. In another system reverse iontophoresis is used for sampling interstitial fluid which reflects capillary blood glucose levels. Instead of using an elec. current, a brandnew system creates micropores in the skin by a laser ablation system. Through these micropores a specific device performs a mild suction to obtain interstitial fluid. Further systems which measure blood glucose by near IR spectroscopy are still investigated to improve their tech. function and to reduce their wt.

ST **diabetes** antidiabetics insulin analog deriv review; blood glucose detn device **diabetes** review; **glucagon like peptide 1** antidiabetic review

IT Blood glucose
RL: ANT (Analyte); BPR (Biological process); ANST (Analytical study); BIOL (Biological study); PROC (Process)
(blood glucose detd. in type 1 **diabetes** mellitus treated with insulin analogs and derivs.)

IT Insulin dependent **diabetes** mellitus
Medical goods
(insulin analogs and derivs., devices and dosage forms treatment of type 1 **diabetes** mellitus)

IT Drug delivery systems
(insulin analogs and derivs., treatment of type 1 **diabetes** mellitus)

IT 89750-14-1, Glucagon-like peptide I
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**GLP-1**, treatment of type 1 **diabetes** mellitus)

IT 9004-10-8, Insulin, biological studies
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(insulin analogs and derivs., treatment of type 1 **diabetes** mellitus)

L5 ANSWER 7 OF 126 CAPLUS COPYRIGHT 1999 ACS

AN 1999:615944 CAPLUS

DN 131:318078

TI **Glucagon-like peptide-1** regulates the beta cell transcription factor, PDX-1, in insulinoma cells

AU Wang, Xiaolin; Cahill, Catherine M.; Pineyro, Marco A.; Zhou, Jie; Doyle, Maire E.; Egan, Josephine M.

CS Diabetes Section and Laboratory of Biological Chemistry (CMC), National Institute on Aging, National Institute of Health, Baltimore, MD, 21224, USA

SO Endocrinology (1999), 140(10), 4904-4907

CODEN: ENDOAO; ISSN: 0013-7227
PB Endocrine Society
DT Journal
LA English
CC 2-6 (Mammalian Hormones)
AB **Glucagon-like peptide-1** (**GLP-1**) enhances insulin biosynthesis and secretion as well as transcription of the insulin, GLUT2 and glucokinase genes. The latter are also regulated by the PDX-1 homeoprotein. We investigated the possibility that **GLP-1** may be having its long-term pleiotropic effects through a hitherto unknown regulation of PDX-1. We found that PDX-1 mRNA level was significantly increased after 2 h and insulin mRNA level was subsequently increased after 3 h of treatment with **GLP-1** (10 nM) in RIN 1046-38 insulinoma cells. Under these exptl. conditions, there was also a 1.6-fold increase in the expression of PDX-1 protein in whole cell and nuclear exts. Overexpression of PDX-1 in these cells confirmed the finding of the wild type cells such that **GLP-1** induced a 2-fold increase in whole cell exts. and a 3-fold increase in nuclear exts. of PDX-1 protein levels. The results of electrophoretic mobility shift expts. showed that PDX-1 protein binding to the A1 element of the rat insulin II promoter was also increased 2 h posttreatment with **GLP-1**. In summary, we have uncovered a previously unknown aspect to the regulation of PDX-1 in beta cells. This has important implications in the physiol. of adult beta cells and the treatment of type 2 **diabetes** mellitus with **GLP-1** or its analogs.
ST glucagon like peptide PDX1 expression insulinoma; GLP1 PDX1 expression insulinoma
IT Promoter (genetic element)
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(A1; **glucagon-like peptide-1** regulation of PDX-1 expression in insulinoma cells and mechanism therefor)
IT Transcription factors
RL: BPR (Biological process); MFM (Metabolic formation); BIOL (Biological study); FORM (Formation, nonpreparative); PROC (Process)
(PDX-1; **glucagon-like peptide-1** regulation of PDX-1 expression in insulinoma cells and mechanism therefor)
IT Gene expression
Transcription, genetic
(**glucagon-like peptide-1** regulation of PDX-1 expression in insulinoma cells and mechanism therefor)
IT Pancreatic islet of Langerhans
(insulinoma; **glucagon-like peptide-1** regulation of PDX-1 expression in insulinoma cells and mechanism therefor)
IT 89750-14-1, Glucagon-like peptide I
RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)
(**glucagon-like peptide-1** regulation of PDX-1 expression in insulinoma cells and mechanism therefor)

L5 ANSWER 8 OF 126 CAPLUS COPYRIGHT 1999 ACS
AN 1999:581094 CAPLUS
DN 131:281647
TI Treatment of type 2 **diabetes** mellitus based on **glucagon-like peptide-1**
AU Holst, Jens Juul
CS Department of Medical Physiology, The Panum Institute, University of Copenhagen, Copenhagen, DK-2200, Den.
SO Expert Opin. Invest. Drugs (1999), 8(9), 1409-1415
CODEN: EOIDER; ISSN: 1354-3784

PB Ashley Publications
DT Journal; General Review
LA English
CC 2-0 (Mammalian Hormones)
AB A review with 58 refs. **Glucagon-like peptide -1** (**GLP-1**) is a peptide hormone released from the gut mucosa in response to meal ingestion. Its actions include stimulation of all steps of insulin gene expression, as well as .beta.-cell growth, inhibition of glucagon secretion, inhibition of hepatic glucose prodn., inhibition of gastrointestinal secretion and motility, and inhibition of appetite and food intake. Physiol., therefore, **GLP-1** is thought to act as an incretin hormone (intestinal hormones that enhance meal-related insulin secretion) and as one of the hormones of the ileal brake mechanism (endocrine inhibition of gastrointestinal motility and secretion in the presence of nutrients in the lower small intestine). However, because of these same actions, the hormone can normalize the blood glucose of patients with Type 2 **diabetes** mellitus, and, in contradistinction to insulin and sulfonylurea, it does not cause hypoglycemia. Therefore, treatment of Type 2 **diabetes** based on **GLP-1** is currently being investigated. As a peptide, it must be administered parenterally, and, in addn., it is metabolized extremely rapidly. However, several methods to circumvent these problems have already been developed. A **GLP-1**-based therapy of **diabetes** mellitus and perhaps also obesity is therefore likely to become a realistic alternative to current therapies of these disorders.
ST review type 2 **diabetes** mellitus **glucagon like peptide 1**
IT Non-insulin-dependent **diabetes** mellitus
(treatment of type 2 **diabetes** mellitus based on **glucagon-like peptide-1**)
IT 89750-14-1, Glucagon-like peptide I
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(treatment of type 2 **diabetes** mellitus based on **glucagon-like peptide-1**)

L5 ANSWER 13 OF 126 CAPLUS COPYRIGHT 1999 ACS
AN 1999:495164 CAPLUS
DN 131:139502
TI Method of regulating glucose metabolism, and reagents related thereto
IN Bachovchin, William W.; Plaut, Andrew G.; Drucker, Daniel J.
PA Trustees of Tufts University, USA
SO PCT Int. Appl., 72 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM A61K031-00
CC 1-10 (Pharmacology)
Section cross-reference(s): 34, 63
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 9938501	A2	19990805	WO 1999-US2294	19990202

W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRAI US 1998-PV73409 19980202
OS MARPAT 131:139502
AB The present invention provides methods and compns. for modification and regulation of glucose and lipid metab., generally to reduce insulin resistance, hyperglycemia, hyperinsulinemia, obesity, hyperlipidemia, hyperlipoproteinemia (such as chylomicrons, VLDL and LDL), and to regulate body fat and more generally lipid stores, and, more generally, for the improvement of metab. disorders, esp. those assocd. with **diabetes**, obesity and/or atherosclerosis.
ST antidiabetic boron peptidomimetic prepn
IT Gastrointestinal hormones
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(PHI, plasma half-life of; method of regulating glucose metab., and reagents related thereto)
IT Antidiabetic agents
Antiobesity agents
Enzyme inhibition kinetics
Hyperglycemia
Hyperinsulinemia
Hyperlipidemia
Hyperlipoproteinemia
Hypolipemic agents
Immunosuppressants
Insulin resistance
Non-insulin-dependent **diabetes** mellitus
Obesity
Oral drug delivery systems
Peptidomimetics
(method of regulating glucose metab., and reagents related thereto)
IT Pharmacokinetics
(of **GLP-1**; method of regulating glucose metab., and reagents related thereto)
IT 9001-92-7, Proteinase 54249-88-6, Dipeptidylpeptidase IV

RL: BSU (Biological study, unclassified); BIOL (Biological study) (inhibitors; method of regulating glucose metab., and reagents related thereto)

IT 50-99-7, Glucose, biological studies 89750-14-1, Glucagon-like peptide I

RL: BPR (Biological process); BIOL (Biological study); PROC (Process) (metab. of; method of regulating glucose metab., and reagents related thereto)

IT 139649-82-4P 139649-83-5P

RL: PNU (Preparation, unclassified); PREP (Preparation) (method of regulating glucose metab., and reagents related thereto)

IT 15761-38-3P 123948-26-5P 123948-27-6P 123948-28-7P 235085-88-8P 235085-95-7P

RL: PNU (Preparation, unclassified); RCT (Reactant); PREP (Preparation) (method of regulating glucose metab., and reagents related thereto)

IT 106-95-6, Allyl bromide, reactions 109-72-8, n-Butyllithium, reactions 999-97-3, Hexamethyldisilazane 4039-32-1

RL: RCT (Reactant) (method of regulating glucose metab., and reagents related thereto)

IT 7440-42-8, Boron, biological studies

RL: BSU (Biological study, unclassified); BIOL (Biological study) (peptidomimetics contg.; method of regulating glucose metab., and reagents related thereto)

IT 1115-78-2, L-Alanine, D-alanyl- 13485-59-1, Alanylproline 20488-28-2, Prolylproline

RL: BSU (Biological study, unclassified); BIOL (Biological study) (peptidomimetics of; method of regulating glucose metab., and reagents related thereto)

IT 9034-39-3, Growth hormone-releasing factor 37221-79-7, Vasoactive intestinal peptide 59392-49-3, Gip 82785-45-3, Neuropeptide Y 89468-62-2, Helodermin 89750-15-2, **Glucagon like peptide 2** 106388-42-5, Peptide YY 137061-48-4, Pacap

RL: BPR (Biological process); BIOL (Biological study); PROC (Process) (plasma half-life of; method of regulating glucose metab., and reagents related thereto)

L5 ANSWER 14 OF 126 CAPLUS COPYRIGHT 1999 ACS

AN 1999:486755 CAPLUS

DN 131:238027

TI **Glucagon-like peptide 1** (**GLP-1**): an intestinal hormone, signalling nutritional abundance, with an unusual therapeutic potential

AU Holst, Jens Juul

CS Department of Medical Physiology, The Panum Institute, University of Copenhagen, Copenhagen, DK-2200, Den.

SO Trends Endocrinol. Metab. (1999), 10(6), 229-235
CODEN: TENME4; ISSN: 1043-2760

PB Elsevier Science Ltd.

DT Journal; General Review

LA English

CC 2-0 (Mammalian Hormones)

AB A review with 74 refs. The incretin hormone, **glucagon-like peptide 1** (**GLP-1**) has many actions; namely: (1) it enhances all steps of insulin biosynthesis and potentiates glucose-induced secretion; (2) it seems to have trophic effects on pancreatic cells; (3) it inhibits glucagon secretion; (4) it inhibits hepatic glucose prodn. and lowers blood glucose, but does not produce severe hypoglycemia; (5) it inhibits postprandial gastrointestinal motility and secretion; and (6) it reduces appetite and food intake. Because of this, current research is focusing upon development of a clin. practicable therapy for type 2 **diabetes** mellitus based on **GLP-1**.

ST GLP1 bioactivity **diabetes** therapy review

IT Antidiabetic agents

Islet of Langerhans
Non-insulin-dependent **diabetes** mellitus
(**GLP-1** bioactivity in relation to type 2 **diabetes** mellitus therapy)

IT 89750-14-1, Glucagon-like peptide I
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**GLP-1** bioactivity in relation to type 2 **diabetes** mellitus therapy)

L5 ANSWER 15 OF 126 CAPLUS COPYRIGHT 1999 ACS
AN 1999:473487 CAPLUS
TI Encapsulated, genetically engineered cells, secreting **glucagon-like peptide-1** for the treatment of non-insulin-dependent **diabetes** mellitus
AU Burcelin, Remy; Rolland, Eric; Dolci, Wanda; Germain, Stephane; Carrel, Veronique; Thorens, Bernard
CS Institute of Pharmacology and Toxicology, University of Lausanne, Lausanne, CH-1005, Switz.
SO Ann. N. Y. Acad. Sci. (1999), 875(Bioartificial Organs II), 277-285
CODEN: ANYAA9; ISSN: 0077-8923
PB New York Academy of Sciences
DT Journal
LA English
CC 63 (Pharmaceuticals)
AB Non-insulin-dependent, or type II, **diabetes** mellitus is characterized by a progressive impairment of glucose-induced insulin secretion by pancreatic .beta. cells and by a relative decreased sensitivity of target tissues to the action of this hormone. About one third of type II diabetic patients are treated with oral hypoglycemic agents to stimulate insulin secretion. These drugs however risk inducing hypoglycemia and, over time, lose their efficacy. An alternative treatment is the use of **glucagon-like peptide -1** (**GLP-1**), a gut peptidic hormone with a strong insulinotropic activity. Its activity depends of the presence of normal blood glucose concns. and therefore does not risk inducing hypoglycemia. **GLP-1** can correct hyperglycemia in diabetic patients, even in those no longer responding to hypoglycemic agents. Because it is a peptide, **GLP-1** must be administered by injection; this may prevent its wide therapeutic use. Here we propose to use cell lines genetically engineered to secrete a mutant form of **GLP-1** which has a longer half-life in vivo but which is as potent as the wild-type peptide. The genetically engineered cells are then encapsulated in semi-permeable hollow fibers for implantation in diabetic hosts for const., long-term, in situ delivery of the peptide. This approach may be a novel therapy for type II **diabetes**.

L5 ANSWER 18 OF 126 CAPLUS COPYRIGHT 1999 ACS
AN 1999:390060 CAPLUS
DN 131:39829
TI **Glucagon-like peptide-1**: a basis for new approaches to the management of **diabetes**
AU Deacon, Carolyn F.; Holst, Jens J.; Carr, Richard D.
CS Department of Medical Physiology, The Panum Institute, University of Copenhagen, Bagsvaerd, Den.
SO Drugs Today (1999), 35(3), 159-170
CODEN: MDACAP; ISSN: 0025-7656
PB Prous Science
DT Journal; General Review
LA English
CC 2-0 (Mammalian Hormones)
Section cross-reference(s): 1
AB A review with 110 refs. Type 2 **diabetes** mellitus is a metabolic disease resulting in raised blood sugar which, if not satisfactorily controlled, can cause severe and often debilitating complications. Unfortunately, for many patients, the existing therapies do not give adequate control. **Glucagon-like peptide-1** (**GLP-1**) is an incretin hormone which has a spectrum of activities which oppose the symptoms of **diabetes**. Of particular significance is the fact that these actions are glucose-dependent, meaning that the risk of severe hypoglycemia is practically eliminated. The recent elucidation of the key role of dipeptidyl peptidase IV in detg. the metabolic stability of **GLP-1** has given the rationale for two novel therapeutic strategies, namely, **GLP-1** analogs which are resistant to the enzyme and inhibitors of the enzyme which boost levels of endogenous intact **GLP-1**. These approaches aim to maximize the therapeutic advantages offered by **GLP-1** and give the hope of providing effective glycemic control without the risk of overt hypoglycemia.
ST review glucagon like peptide antidiabetic NIDDM
IT Antidiabetic agents
Non-insulin-dependent **diabetes** mellitus
(**glucagon-like peptide-1** for management of human **diabetes**)
IT 89750-14-1, Glucagon-like peptide I
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**glucagon-like peptide-1** for management of human **diabetes**)

L5 ANSWER 21 OF 126 CAPLUS COPYRIGHT 1999 ACS
AN 1999:341597 CAPLUS
DN 131:97841
TI **Glucagon-like peptide-1** promotes satiety and reduces food intake in patients with **diabetes** mellitus type 2
AU Gutzwiller, Jean-Pierre; Drewe, Jurgen; Goke, Burkhard; Schmidt, Harald; Rohrer, Beat; Lareida, Jurg; Beglinger, Christoph
CS Department of Internal Medicine, Kantonsspital, Aarau, CH-5000, Germany
SO Am. J. Physiol. (1999), 276(5, Pt. 2), R1541-R1544
CODEN: AJPHAP; ISSN: 0002-9513
PB American Physiological Society
DT Journal
LA English
CC 2-6 (Mammalian Hormones)
AB **Glucagon-like peptide-1**-(7-36) amide (**GLP-1**) is an incretin hormone of the enteroinsular axis. Recent exptl. evidence in animals and healthy subjects suggests that **GLP-1** has a role in controlling appetite and energy intake in humans. The authors have therefore examd. in a double-blind, placebo-controlled, crossover study in 12 patients with **diabetes** type 2 the effect of i.v. infused **GLP-1** on appetite sensations and energy intake. On 2 days, either saline or **GLP-1** (1.5 pmol.cntdot.kg-1.cntdot.min-1) was given throughout the expt. Visual analog scales were used to assess appetite sensations; furthermore, food and fluid intake of a test meal were recorded, and blood was sampled for anal. of plasma glucose and hormone levels. **GLP-1** infusion enhanced satiety and fullness compared with placebo (P = 0.028 for fullness and P = 0.026 for hunger feelings). Energy intake was reduced by 27% by **GLP-1** (P = 0.034) compared with saline. The results demonstrate a marked effect of **GLP-1** on appetite by showing enhanced satiety and reduced energy intake in patients with **diabetes** type 2.
ST **glucagon like peptide 1** satiety food intake **diabetes** mellitus
IT Appetite
Feeding (behavior)
Non-insulin-dependent **diabetes** mellitus
Satiety
(**glucagon-like peptide-1** promotes satiety and reduces food intake in patients with **diabetes** mellitus type 2)
IT Blood glucose
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(**glucagon-like peptide-1** promotes satiety and reduces food intake in patients with **diabetes** mellitus type 2)
IT 89750-14-1, Glucagon-like peptide I 118549-37-4, Insulinotropin
RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)
(**glucagon-like peptide-1** promotes satiety and reduces food intake in patients with **diabetes** mellitus type 2)
IT 9004-10-8, Insulin, biological studies 9007-92-5, Glucagon, biological studies
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(**glucagon-like peptide-1** promotes satiety and reduces food intake in patients with

L5 ANSWER 26 OF 126 CAPLUS COPYRIGHT 1999 ACS
AN 1999:214954 CAPLUS
DN 131:943
TI Glucose-dependent stimulatory effect of **glucagon-like peptide 1**(7-36) amide on the electrical activity of pancreatic .beta.-cells recorded in vivo
AU Fernandez, Juana; Valdeolmillos, Miguel
CS Instituto de Neurociencias, Campus de San Juan, Universidad Miguel Hernandez, San Juan de Alicante, 03550, Spain
SO Diabetes (1999), 48(4), 754-757
CODEN: DIAEAZ; ISSN: 0012-1797
PB American Diabetes Association
DT Journal
LA English
CC 2-6 (Mammalian Hormones)
AB The stimulatory effect of the glucagon-like peptide (**GLP**)-**1**(7-36) amide on elec. activity in pancreatic .beta.-cells recorded in vivo was studied. The injection of **GLP-1** produces a lengthening of the active phase with respect to the silent phase, leading to a stimulation of insulin release, which produces a secondary decrease in blood glucose concn. and eventually, to the hyperpolarization of the membrane at a blood glucose level of .apprx.5 mmol/L. The injection of **GLP-1** at a glycemic level <5 mmol/L does not stimulate elec. activity. This is in contrast to the effect of tolbutamide, which stimulates elec. activity at low glucose concns. These results demonstrate that in vivo, the stimulatory effect of **GLP-1** on insulin secretion is at least partially mediated by its effect on .beta.-cell elec. activity. Furthermore, the glucose dependence of the effect confers to **GLP-1**, a security factor that supports its potential use in the treatment of type 2 **diabetes**.
ST glucagonlike peptide 1 pancreatic beta cell elec activity
IT Electric activity (biological)
.beta.-Cell
(glucose-dependent stimulatory effect of **glucagon-like peptide 1** (7-36) amide on elec. activity of pancreatic .beta.-cells recorded in vivo)
IT Hyperpolarization (biological)
(glucose-dependent stimulatory effect of **glucagon-like peptide 1** (7-36) amide on pancreatic .beta.-cell elec. activity and insulin secretion in vivo)
IT Blood glucose
RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)
(glucose-dependent stimulatory effect of **glucagon-like peptide 1** (7-36) amide on pancreatic .beta.-cell elec. activity and insulin secretion in vivo)
IT 50-99-7, D-Glucose, biological studies 118549-37-4, Insulinotropin
RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)
(glucose-dependent stimulatory effect of **glucagon-like peptide 1** (7-36) amide on elec. activity of pancreatic .beta.-cells recorded in vivo)
IT 9004-10-8, Insulin, biological studies
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(glucose-dependent stimulatory effect of **glucagon-like peptide 1** (7-36) amide on pancreatic .beta.-cell elec. activity and insulin secretion in vivo)

L5 ANSWER 32 OF 126 CAPLUS COPYRIGHT 1999 ACS
AN 1999:69175 CAPLUS
DN 130:262214
TI On the treatment of **diabetes** mellitus with **glucagon-like peptide-1**
AU Holst, Jens Juul; Deacon, Carolyn; Toft-Nielsen, Maj-Brit; Bjerre-Knudsen, Lotte
CS Department of Medical Physiology, The Panum Institute, University of Copenhagen, Copenhagen, DK-2200, Den.
SO Ann. N. Y. Acad. Sci. (1998), 865(VIP, PACAP, and Related Peptides), 336-343
CODEN: ANYAA9; ISSN: 0077-8923
PB New York Academy of Sciences
DT Journal; General Review
LA English
CC 2-0 (Mammalian Hormones)
Section cross-reference(s): 63
AB A review with 37 refs. As a therapeutic principle, the insulinotropic peptide, **GLP-1**, of the secretin-glucagon family of peptides, has turned out to possess some remarkably attractive properties, including the capability of normalizing blood glucose concns. in patients with non-insulin-dependent **diabetes** mellitus and promoting satiety and reducing food intake in healthy volunteers. Because of rapid and extensive metabolization, the peptide is not immediately clin. applicable and, as a therapeutic principle, **GLP-1** is still in its infancy. Some possible avenues for circumventing these difficulties are the development of DPP-IV-resistant analogs, the inhibition of DPP-IV, enhancement of **GLP-1** secretion, GLP delivery systems using continuous s.c. infusion or buccal tablets, **GLP-1** absorption, and orally active, stable analogs. It seems likely that one or more of these approaches could result in a clin. useful development program.
ST **diabetes** mellitus glucagonlike peptide review; antidiabetic GLPI review
IT Antidiabetic agents
Drug delivery systems
(**diabetes** mellitus therapy with **glucagon-like peptide-1**)
IT 89750-14-1, Glucagon-like peptide I
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**diabetes** mellitus therapy with **glucagon-like peptide-1**)

L5 ANSWER 33 OF 126 CAPLUS COPYRIGHT 1999 ACS
AN 1999:36687 CAPLUS
DN 130:205386
TI **Glucagon-like peptide-1** has no insulin-like effects in insulin-dependent diabetic dogs maintained normoglycemic and normoinsulinemic
AU Freyse, E.-J.; Knospe, S.; Becher, T.; El Hag, O.; Goke, B.; Fischer, U.
CS Diabetes Institute "Gerhardt Katsch,", Karlsburg, D-17495, Germany
SO Metab., Clin. Exp. (1999), 48(1), 134-137
CODEN: METAAJ; ISSN: 0026-0495
PB W. B. Saunders Co.
DT Journal
LA English
CC 2-6 (Mammalian Hormones)

Section cross-reference(s): 14

AB A pharmacol. concn. of **glucagon-like peptide -1** (**GLP-1**) in the insulin-deficient state clearly decreases the blood glucose level. Therefore, this study was designed to evaluate a putatively relevant effect of the gastrointestinal peptide as an adjuvant to insulin replacement therapy. **GLP-1** (**GLP-1**(7-36) amide 10 pmol/kg/min) was infused i.v. over 8 h in nine fasting, C-peptide-neg. diabetic dogs. The animals were under normoglycemic control by glucose-controlled insulin infusion (GCII) during the night before and during **GLP-1** administration. During the paired control tests, the animals received saline infusion instead of **GLP-1**. In addn. to the insulin infusion rates required to maintain normoglycemia, hormones, metabolites, and the turnover rates for glucose (6-3H-glucose), alanine (U-14C-alanine), and urea (15N2-urea) were measured during the final 2 h of **GLP-1** administration. Circulating plasma **GLP-1** levels increased from 3 to 17 pmol/L. There was no significant difference in the insulin infusion rate between the exptl. and control groups (0.43 v 0.40 mU/kg/h, av. over the entire interval). Glycemia was maintained at a practically identical level (4.9 v 4.8 mmol/L). Also, the concn. of plasma insulin-which was not hyperinsulinemic-and pancreatic glucagon remained unaltered. The authors found no appreciable effect of **GLP-1** on glucose prodn. and metabolic clearance, alanine turnover and the formation of glucose from alanine (1.8 v 1.4 .mu.mol/kg/min), or the urea prodn. rate as a measure of overall amino acid catabolism (4.1 v 4.1 .mu.mol/kg/min). Thus, no conclusive adjuvant effect of **GLP-1** was ascertained in insulin-treated diabetic dogs under normoglycemic control.

ST GLP insulin **diabetes**

IT Antidiabetic agents
Insulin dependent **diabetes** mellitus
(**GLP-1** effect on insulin activity in insulin-dependent diabetic dogs maintained normoglycemic and normoinsulinemic)

IT Amino acids, biological studies
Blood glucose
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(**GLP-1** effect on insulin activity in insulin-dependent diabetic dogs maintained normoglycemic and normoinsulinemic)

IT 9004-10-8, Insulin, biological studies
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(**GLP-1** effect on insulin activity in insulin-dependent diabetic dogs maintained normoglycemic and normoinsulinemic)

IT 89750-14-1, Glucagon-like peptide I
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**GLP-1** effect on insulin activity in insulin-dependent diabetic dogs maintained normoglycemic and normoinsulinemic)

IT 56-41-7, Alanine, biological studies 57-13-6, Urea, biological studies 9007-92-5, Glucagon, biological studies
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(**GLP-1** effect on insulin activity in insulin-dependent diabetic dogs maintained normoglycemic and normoinsulinemic)

L5 ANSWER 34 OF 126 CAPLUS COPYRIGHT 1999 ACS

AN 1999:26082 CAPLUS

DN 130:76267

TI Effects of gastrointestinal hormone on insulin secretion. **GLP-1**

AU Mizuno, Akira; Shima, Kenji
CS Sch. Med., Univ. Tokushima, Tokushima, 770, Japan
SO Diabetes Front. (1998), 9(6), 716-720
CODEN: DIFREZ; ISSN: 0915-6593
PB Medikaru Rebyusha
DT Journal; General Review
LA Japanese
CC 2-0 (Mammalian Hormones)
Section cross-reference(s): 14
AB A review, with 27 refs., on mechanism of **GLP-1** (**glucagon-like peptide-1**)-stimulated insulin secretion in pancreatic B-cells, action of **GLP-1** and Ca2+ channel, glucose-dependent insulin secretion stimulation and **GLP-1**, and hypoglycemic action of **GLP-1** on diabetic patients.
ST review glucagonlike peptide 1 insulin secretion; **diabetes** insulin secretion GLP1 hypoglycemic review
IT **Diabetes** mellitus
(effects of gastrointestinal hormone, **GLP-1**, on insulin secretion)
IT 89750-14-1, Glucagon-like peptide I
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(effects of gastrointestinal hormone, **GLP-1**, on insulin secretion)
IT 9004-10-8, Insulin, biological studies
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(effects of gastrointestinal hormone, **GLP-1**, on insulin secretion)

L5 ANSWER 36 OF 126 CAPLUS COPYRIGHT 1999 ACS
AN 1998:719697 CAPLUS
DN 129:310971
TI **Glucagon-like peptide 1** (**GLP-1**). A potent gut hormone with a possible therapeutic perspective
AU Nauck, M. A.
CS Department Medicine, Knappschafts-Krankenhaus, Ruhr-University, Bochum, D-44892, Germany
SO Acta Diabetol. (1998), 35(3), 117-129
CODEN: ACDAEZ; ISSN: 0940-5429
PB Springer-Verlag
DT Journal; General Review
LA English
CC 2-0 (Mammalian Hormones)
AB A review with 166 refs. **Glucagon-like peptide 1** (**GLP-1**) is a physiol. incretin hormone from the lower gastrointestinal tract, partially explaining the augmented insulin response after oral compared to i.v. glucose administration in normal humans. **GLP-1** also lowers glucagon concns., slows gastric emptying, stimulates (pro)insulin biosynthesis, and reduces food intake upon intracerebroventricular administration in animals. Therefore, **GLP-1** offers some interesting perspective for the treatment of type 2, and perhaps also for type 1 diabetic patients. **GLP-1** glucose-dependently stimulates insulin secretion in type-2 diabetic patients and exogenous administration of **GLP-1** ([7-37] or [7-36 amide]) in doses elevating plasma concns. to approx. 3-4 times physiol. postprandial levels fully normalizes fasting hyperglycemia and reduces postprandial glycemic increments. Due to rapid proteolytic cleavage, which results in an inactive or even antagonistic fragment, **GLP-1** [9-36 amide], and to rapid elimination, the half-life of **GLP-1** is too short to maintain therapeutic plasma levels for sufficient period by s.c. injections of the natural peptide hormone. Current research aims to characterize **GLP-1** analogs with more suitable pharmacokinetic properties than the original peptide. Given the large amt. of **GLP-1** present in L cells, it also appears worthwhile to search for more agents that could mobilize this endogenous pool of **GLP-1**.
ST review **glucagon like peptide 1** **diabetes**; GLP1 incretin hormone **diabetes** review
IT Insulin dependent **diabetes** mellitus
Intestinal mucosa
Non-insulin-dependent **diabetes** mellitus
Pancreas
(**glucagon-like peptide 1** is a potent gut hormone with a possible therapeutic perspective)
IT Gastrointestinal hormones
RL: BAC (Biological activity or effector, except adverse); BOC (Biological occurrence); BIOL (Biological study); OCCU (Occurrence)
(**glucagon-like peptide 1** is a potent gut hormone with a possible therapeutic perspective)
IT 89750-14-1, Glucagon-like peptide I
RL: BAC (Biological activity or effector, except adverse); BOC (Biological occurrence); BPR (Biological process); BIOL (Biological study); OCCU (Occurrence); PROC (Process)
(**glucagon-like peptide 1** is a

potent gut hormone with a possible therapeutic perspective)

IT 54241-84-8, Incretin
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(**glucagon-like peptide 1** is a
potent gut hormone with a possible therapeutic perspective)

L5 ANSWER 38 OF 126 CAPLUS COPYRIGHT 1999 ACS
AN 1998:682139 CAPLUS
DN 129:276356
TI **Glucagon-like peptide-1** analogs
IN Hoffmann, James A.
PA Eli Lilly and Co., USA
SO PCT Int. Appl., 26 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM A61K038-00
CC 34-3 (Amino Acids, Peptides, and Proteins)
Section cross-reference(s): 1
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9843658	A1	19981008	WO 1998-US5945	19980325
	W: AL, AM, AU, AZ, BA, BB, BG, BR, BY, CA, CN, CU, CZ, EE, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, RU, SD, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
	AU 9865862	A1	19981022	AU 1998-65862	19980325
PRAI	US 1997-41167		19970331		
	WO 1998-US5945		19980325		

OS MARPAT 129:276356
AB **Glucagon-like peptide-1** (**GLP-1**) analogs R1-X-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-

Ser-Tyr-Leu-Y-Gly-Gln-Ala-Ala-Lys-Z-Phe-Ile-Ala-Trp-Leu-Val-Lys-Gly-Arg-R2 (R1 = His, D-His, desamino-, 2-amino-, or .beta.-hydroxyhistidine, homohistidine, .alpha.-fluoromethyl- or .alpha.-methylhistidine; X = Met, Asp, Lys, Thr, Leu, Asn, Gln, Phe, Val, or Tyr; Y and Z = Glu, Gln, Ala, Thr, Ser, Gly; R2 = NH2, Gly-OH) were prepd. for treating **diabetes**. Thus, Met-8 **GLP-1**(7-36)NH2 was synthesized by the solid phase method and showed 16.6.+-.5.8% receptor affinity in the cAMP assay.
ST **glucagon like peptide 1** analog
prepn
IT Antidiabetic agents
(prepn. of **glucagon-like peptide-1** analogs)
IT Peptides, preparation
RL: BAC (Biological activity or effector, except adverse); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of **glucagon-like peptide-1** analogs)
IT 89750-14-1DP, Glucagon-like peptide I, analogs 213754-29-1P 213754-31-5P 213754-33-7P 213754-35-9P
RL: BAC (Biological activity or effector, except adverse); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of **glucagon-like peptide-1** analogs)

L5 ANSWER 41 OF 126 CAPLUS COPYRIGHT 1999 ACS
AN 1998:606686 CAPLUS
DN 129:311091
TI The effect of glucose and **glucagon-like peptide-1** stimulation on insulin release in the perfused pancreas in a non-insulin-dependent **diabetes** mellitus animal model
AU Shen, Hua-Qiong; Roth, Mark D.; Peterson, Richard G.
CS Department of Anatomy, Indiana University School of Medicine, Indianapolis, IN, USA
SO Metab., Clin. Exp. (1998), 47(9), 1042-1047
CODEN: METAAJ; ISSN: 0026-0495
PB W. B. Saunders Co.
DT Journal
LA English
CC 2-6 (Mammalian Hormones)
Section cross-reference(s): 14
AB This study was designed to investigate the effect of **glucagon-like peptide-1** (**GLP-1**) on pancreatic .beta.-cell function in normal, Zucker diabetic fatty (ZDF) rats, a model for non-insulin-dependent **diabetes** mellitus (NIDDM or type II **diabetes**) and their heterozygous siblings. Pancreas perfusion and ELISA were used to detect the changes in insulin release under fasting and hyperglycemic conditions and following stimulation with **GLP-1**. Animals from the ZDF/Gmi-fa rats (ZDF) were grouped according to age, sex, and phenotype (obese or lean), and compared with LA lean rats. Glucose stimulation (10 mmol/L) in obese rats showed repressed response in insulin release. Glucose plus **GLP-1** stimulation caused increased insulin release in all groups. The degree of this response differed between groups: lean > obese; young > adult; female > male. The LA lean control group was most sensitive, while the ZDF overtly diabetic group had the lowest response. In addn., the pulsatile pattern of insulin secretion was suppressed in ZDF rats, esp. in obese groups. These results support the hypothesis that **GLP-1** can effectively stimulate insulin secretion. Insulin release was defective in ZDF obese rats and could be partially restored with **GLP-1**. ZDF lean rats also showed suppression of .beta.-cell function and there was a difference in .beta.-cell function related to sex in ZDF strain. This study documents the efficacy of **GLP-1** to stimulate insulin release and contributes to the authors' understanding of the pathophysiol. mechanisms underlying NIDDM.
ST glucose GLP insulin pancreas **diabetes** model
IT Development (mammalian postnatal)
Hyperglycemia
Non-insulin-dependent **diabetes** mellitus
Obesity
Sex differences
.beta.-Cell
(glucose and **GLP-1** stimulation of insulin release in perfused pancreas in non-insulin-dependent **diabetes** mellitus animal model)
IT 50-99-7, Glucose, biological studies 89750-14-1, Glucagon-like peptide I
RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)
(glucose and **GLP-1** stimulation of insulin release

in perfused pancreas in non-insulin-dependent **diabetes** mellitus animal model)

IT 9004-10-8, Insulin, biological studies
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(glucose and **GLP-1** stimulation of insulin release in perfused pancreas in non-insulin-dependent **diabetes** mellitus animal model)

L5 ANSWER 49 OF 126 CAPLUS COPYRIGHT 1999 ACS
AN 1998:350688 CAPLUS
DN 129:76809
TI Effects of **glucagon-like peptide 1** on the kinetics of glycogen synthase a in hepatocytes from normal and diabetic rats
AU Lopez-Delgado, Maria I.; Morales, Monica; Villanueva-Penacarrillo, Maria L.; Malaisse, Willy J.; Valverde, Isabel
CS Department of Metabolism, Nutrition and Hormones, Fundacion Jimenez Diaz, Madrid, 28040, Spain
SO Endocrinology (1998), 139(6), 2811-2817
CODEN: ENDOAO; ISSN: 0013-7227
PB Endocrine Society
DT Journal
LA English
CC 2-6 (Mammalian Hormones)
AB **Glucagon-like peptide 1**(7-36)amide (**GLP-1**) is currently under investigation as a possible tool in the treatment of non-insulin-dependent **diabetes** mellitus. In addn. to enhancing nutrient-stimulated insulin release, the peptide also favors glycogen synthesis and glucose use in liver, muscle, and adipose tissue. **GLP-1** also activates glycogen synthase a in hepatocytes from both normal and diabetic rats. In the present study, the kinetic aspects of such an activation were investigated in hepatocytes from normal rats and from animals rendered diabetic induced by injection of streptozotocin, either in the adult age (insulin-dependent **diabetes** mellitus model) or in days 1 or 5 after birth (non-insulin-dependent **diabetes** mellitus models). **GLP -1** increased, in a dose-dependent manner, glycogen synthase a activity in the hepatocytes from all groups studied. The activation of the enzyme reached a steady state within 1 min exposure to **GLP-1**, which, at 10-12 M, caused a half-maximal activation. When comparing fed vs. overnight-starved normal rats, a somewhat lower basal activity of glycogen synthase a in fasted animals coincided with a greater relative increment in reaction velocity in response to **GLP-1**. The basal activity of glycogen synthase a and the relative extent of its inhibition by glucagon or activation by insulin and **GLP-1** were modulated by the extracellular concn. of D-glucose. The activation of glycogen synthase a by either insulin or **GLP-1** resulted not solely in an increase in maximal velocity but also in a decrease in affinity of the enzyme for uridine diphosphate-glucose; in diabetic animals, the capacity of insulin or **GLP-1** to increase the maximal velocity and Michaelis-Menten const. were less marked than in normal rats. In conclusion, this study indicates that the **GLP-1** -induced activation of glycogen synthase a displays attributes of rapidity, sensitivity, and nutritional dependency that are well suited for both participation in the physiol. regulation of enzyme activity and therapeutic purpose.
ST **GLP 1** glycogen synthase hepatocyte **diabetes**
IT Enzyme kinetics
Hepatocyte
Insulin dependent **diabetes** mellitus
Non-insulin-dependent **diabetes** mellitus
Nutrition (animal)

(**glucagon-like peptide 1**
effects on kinetics of glycogen synthase in hepatocytes from normal and
diabetic rats)
IT 9014-56-6, Glycogen synthase 9035-74-9, Glycogen phosphorylase
RL: BAC (Biological activity or effector, except adverse); BPR (Biological
process); BIOL (Biological study); PROC (Process)
(a; **glucagon-like peptide 1**
effects on kinetics of glycogen synthase in hepatocytes from normal and
diabetic rats)
IT 9004-10-8, Insulin, biological studies 16941-32-5, Glucagon (swine)
118549-37-4, Insulinotropin
RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)
(**glucagon-like peptide 1**
effects on kinetics of glycogen synthase in hepatocytes from normal and
diabetic rats)
IT 50-99-7, D-Glucose, biological studies 133-89-1, UDP-glucose
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(**glucagon-like peptide 1**
effects on kinetics of glycogen synthase in hepatocytes from normal and
diabetic rats)

L5 ANSWER 50 OF 126 CAPLUS COPYRIGHT 1999 ACS
AN 1998:323152 CAPLUS
DN 129:8575
TI Use of **glucagon-like peptide-1**
analogs and derivatives administered peripherally in regulation of obesity
IN Dimarchi, Richard D.; Efendic, Suad
PA Eli Lilly and Co., USA
SO PCT Int. Appl., 42 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM A61K038-26
ICS C07K014-605
CC 63-5 (Pharmaceuticals)
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9819698	A1	19980514	WO 1997-US20114	19971104
	W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
	AU 9852457	A1	19980529	AU 1998-52457	19971104
	EP 946191	A1	19991006	EP 1997-947357	19971104
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
	NO 9902557	A	19990615	NO 1999-2557	19990527

PRAI US 1996-30213 19961105
US 1997-961405 19971030
WO 1997-US20114 19971104

AB This invention relates to the use of glucagon-like peptides such as **GLP-1** (**glucagon-like peptide -1**), a **GLP-1** analog, or a **GLP-1** deriv. in methods and compns. for reducing body wt.

ST antiobesity glucagon like peptide sequence
IT Antiobesity agents
Injections (drug delivery systems)
Non-insulin-dependent **diabetes** mellitus
Signal transduction (biological)
(**glucagon-like peptide-1**
analogs and derivs. administered peripherally in regulation of obesity)
IT 89750-14-1DP, Glucagon-related peptide I, analogs 89750-14-1P, Glucagon-related peptide I 106612-94-6P 119637-73-9P
RL: BAC (Biological activity or effector, except adverse); PEP (Physical, engineering or chemical process); PNU (Preparation, unclassified); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); PROC (Process); USES (Uses)
(**glucagon-like peptide-1**
analogs and derivs. administered peripherally in regulation of obesity)
IT 9004-10-8, Insulin, biological studies
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**glucagon-like peptide-1**
analogs and derivs. administered peripherally in regulation of obesity)

L5 ANSWER 51 OF 126 CAPLUS COPYRIGHT 1999 ACS
AN 1998:284593 CAPLUS
DN 129:104945
TI The human **glucagon-like peptide-1** (**GLP-1**) receptor: cloning and functional expression
AU Dillon, Joseph S.; Wheeler, Michael B.; Leng, Xing-Hong; Ligon, B. Brooke;
Boyd, Aubrey E., III
CS Division of Endocrinology, Diabetes, Metabolism and Molecular Medicine, New England Medical Center, Tufts University School of Medicine, Boston, MA, 02111, USA
SO Adv. Exp. Med. Biol. (1997), 426(Physiology and Pathophysiology of the Islets of Langerhans), 113-119
CODEN: AEMBAP; ISSN: 0065-2598
PB Plenum Publishing Corp.
DT Journal
LA English
CC 3-3 (Biochemical Genetics)
Section cross-reference(s): 2, 13
AB Because of the potential therapeutic value of **glucagon-like peptide-1** (**GLP-1**) in the treatment of Non-insulin-dependent **diabetes** mellitus the authors have cloned a human pancreatic islet cDNA encoding a 463 amino acid high affinity **GLP-1** receptor. It was demonstrated that the **GLP-1** receptor was assocd. with second messenger pathways and expressed in the pancreas.
ST human glucagon like peptide receptor sequence; GLP1 receptor human expression signal transduction; pancreas islet expression GLP1 receptor human
IT Protein sequences
Second messenger system
(human **glucagon-like peptide-1** (**GLP-1**) receptor relating cloning and functional expression)
IT **Glucagon-like peptide-1** receptors
RL: BAC (Biological activity or effector, except adverse); PRP (Properties); BIOL (Biological study)
(human **glucagon-like peptide-1** (**GLP-1**) receptor relating cloning and functional expression)
IT Gene expression
Islet of Langerhans

(pancreas-specific gene expression; human **glucagon-like peptide-1 (GLP-1)** receptor relating cloning and functional expression)

IT 14127-61-8, Ca2+, biological studies
RL: BOC (Biological occurrence); BPR (Biological process); BIOL (Biological study); OCCU (Occurrence); PROC (Process)
(**GLP-1** receptor signals through adenylyl cyclase and accumulation of intracellular calcium; human **glucagon-like peptide-1 (GLP-1)** receptor relating cloning and functional expression)

IT 9012-42-4, Adenylyl cyclase
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(**GLP-1** receptor signals through adenylyl cyclase and accumulation of intracellular calcium; human **glucagon-like peptide-1 (GLP-1)** receptor relating cloning and functional expression)

IT 152744-66-6
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)
(amino acid sequence; human **glucagon-like peptide-1 (GLP-1)** receptor relating cloning and functional expression)

IT 89750-14-1, Glucagon-related peptide I
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(human **glucagon-like peptide-1 (GLP-1)** receptor relating cloning and functional expression)

L5 ANSWER 59 OF 126 CAPLUS COPYRIGHT 1999 ACS
AN 1998:77348 CAPLUS
DN 128:188778
TI Mechanisms of the antidiabetic action of subcutaneous **glucagon-like peptide-1**(7-36)amide in non-insulin dependent **diabetes** mellitus
AU Schirra, J.; Leicht, P.; Hildebrand, P.; Beglinge, C.; Arnold, R.; Goke, B.; Katschinski, M.
CS Clinical Research Unit of Gastrointestinal Endocrinology, Department of Gastroenterology and Endocrinology, Philipps-University, Marburg, 35033, Germany
SO J. Endocrinol. (1998), 156(1), 177-186
CODEN: JOENAK; ISSN: 0022-0795
PB Journal of Endocrinology
DT Journal
LA English
CC 2-6 (Mammalian Hormones)
AB Twelve patients with non-insulin dependent **diabetes** mellitus (NIDDM) under secondary failure to sulfonylureas were studied to evaluate the effects of s.c. **glucagon-like peptide-1**(7-36)amide (**GLP-1**) on (a) the gastric emptying pattern of a solid meal (250 kcal) and (b) the glycemic and endocrine responses to this solid meal and an oral glucose tolerance test (OGTT, 300 kcal). **GLP-1** (0.5 nmol/kg) or placebo were s.c. injected 20 min after meal ingestion. **GLP-1** modified the pattern of gastric emptying by prolonging the time to reach maximal emptying velocity (lag period) which was followed by an acceleration in the post-lag period. The maximal emptying velocity and the emptying half-time remained unaltered. With both meals, **GLP-1** diminished the postprandial glucose peak, and reduced the glycemic response during the first two postprandial hours by 54.5% (solid meal) and 32.7% (OGTT). **GLP-1** markedly stimulated insulin secretion with an effect lasting for 105 min (solid meal) or 150 min (OGTT). The post-prandial increase of plasma glucagon was abolished by **GLP-1**. **GLP-1** diminished the postprandial release of pancreatic polypeptide. The initial and transient delay of gastric emptying, the enhancement of postprandial insulin release, and the inhibition of postprandial glucagon release were independent determinants of the post-prandial glucose response after s.c. **GLP-1**. An inhibition of efferent vagal activity may contribute to the inhibitory effect of **GLP-1** on gastric emptying.
ST antidiabetic **GLP 1**; glucagon like peptide antidiabetic
IT Antidiabetic agents
Gastric emptying
Non-insulin-dependent **diabetes** mellitus
(**GLP-1** mechanisms of antidiabetic action after s.c. administration in non-insulin dependent **diabetes** mellitus in human)
IT 50-99-7, D-Glucose, biological studies
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BIOL (Biological study); PROC (Process)
(**GLP-1** mechanisms of antidiabetic action after s.c. administration in non-insulin dependent **diabetes** mellitus in human)
IT 118549-37-4, Insulinotropin
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(**GLP-1** mechanisms of antidiabetic action after s.c. administration in non-insulin dependent **diabetes** mellitus in human)

IT 9004-10-8, Insulin, biological studies 9007-92-5, Glucagon, biological studies 59763-91-6, Pancreatic polypeptide
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(**GLP-1** mechanisms of antidiabetic action after s.c. administration in non-insulin dependent **diabetes** mellitus in human)

L5 ANSWER 60 OF 126 CAPLUS COPYRIGHT 1999 ACS
AN 1998:41714 CAPLUS
DN 128:111161
TI Glucagon-like insulinotropic peptides, compositions and methods
IN Galloway, John A.; Hoffmann, James A.
PA Eli Lilly and Company, USA
SO U.S., 8 pp. Cont.-in-part of U.S. Ser. No. 164,277, abandoned.
CODEN: USXXAM
DT Patent
LA English
IC ICM A61K038-26
ICS C07K014-605
NCL 514012000
CC 2-6 (Mammalian Hormones)
Section cross-reference(s): 63
FAN.CNT 3

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 5705483	A	19980106	US 1995-407831	19950321
	CA 2137206	AA	19950610	CA 1994-2137206	19941202
	JP 07196695	A2	19950801	JP 1994-303404	19941207
	ZA 9504141	A	19961122	ZA 1995-4141	19950522
	NO 9502034	A	19960923	NO 1995-2034	19950523
	EP 733644	A1	19960925	EP 1995-303423	19950523
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, NL, PT, SE				
	HU 74729	A2	19970228	HU 1995-1508	19950523
	CA 2150080	AA	19960922	CA 1995-2150080	19950524
	FI 9502536	A	19960922	FI 1995-2536	19950524
	AU 9520268	A1	19961003	AU 1995-20268	19950524
	AU 708159	B2	19990729		
	CN 1131674	A	19960925	CN 1995-105569	19950526
	JP 08269097	A2	19961015	JP 1995-127910	19950526
	BR 9503036	A	19970923	BR 1995-3036	19950630
	US 5977071	A	19991102	US 1997-927227	19970910
PRAI	US 1993-164277	19931209			
	US 1995-407831	19950321			

OS MARPAT 128:111161
AB The present invention provides novel complexes consisting of certain **GLP-1** mols. assocd. with a divalent metal cation that is capable of co-pptg. with a **GLP-1** mol. Pharmaceutical compns. and methods of using such complexes for enhancing the expression of insulin in B-type islet cells is claimed, as is a method for treating maturity onset **diabetes** mellitus in mammals, particularly humans.
ST GLP1 metal complex prepn insulinotropic
IT Divalent cations
(complexes, with **GLP-1** analogs; prepn. and formulation of glucagon-like insulinotropic peptides)
IT Antidiabetic agents
Drug delivery systems
Non-insulin-dependent **diabetes** mellitus
(prepn. and formulation of glucagon-like insulinotropic peptides)
IT Coordination compounds
RL: BAC (Biological activity or effector, except adverse); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(with **GLP-1** analogs; prepn. and formulation of glucagon-like insulinotropic peptides)

IT 7440-66-6DP, Zinc, complexes with **GLP-1** analogs
7646-85-7DP, Zinc chloride, complexes with **GLP-1** analogs 89750-14-1DP, Glucagon-related peptide I, analogs, divalent metal complexes 107444-51-9DP, Human **glucagon like peptide-1** (7-36) amide, complexes with divalent cations 194551-05-8DP, complexes with divalent metal cations
RL: BAC (Biological activity or effector, except adverse); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. and formulation of glucagon-like insulinotropic peptides)

IT 9004-10-8, Insulin, biological studies
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(prepn. and formulation of glucagon-like insulinotropic peptides)

L5 ANSWER 63 OF 126 CAPLUS COPYRIGHT 1999 ACS
AN 1998:14561 CAPLUS
DN 128:123968
TI No correlation between insulin and islet amyloid polypeptide after stimulation with **glucagon-like peptide-1** in type 2 **diabetes**
AU Ahren, Bo; Gutniak, Mark
CS Dep. Med., Lund Univ., Stockholm, Swed.
SO Eur. J. Endocrinol. (1997), 137(6), 643-649
CODEN: EJOEEP; ISSN: 0804-4643
PB BioScientifica
DT Journal
LA English
CC 2-6 (Mammalian Hormones)
AB The objective of this study was to examine whether **glucagon-like peptide-1** (**GLP-1**), which has been suggested as a new therapeutic agent in type 2 **diabetes**, affects circulating islet amyloid polypeptide (IAPP), a .beta.-cell peptide of potential importance for **diabetes** pathophysiol. **GLP-1** was administered in a buccal tablet (400 .mu.g) to seven healthy subjects and nine subjects with type 2 **diabetes**. Serum IAPP and insulin levels were measured before and after **GLP-1** administration. In the fasting state, serum IAPP was 4.1 pmol/L in the controls vs. 9.8 pmol/L in the subjects with type 2 **diabetes**. IAPP correlated with insulin only in controls (r=0.74) but not in type 2 **diabetes** (r=0.26). At 15 min after **GLP-1**, circulating IAPP increased to 6.0 pmol/L in controls and to 13.8 pmol/L in type 2 **diabetes**. In both groups, serum insulin increased and blood glucose decreased compared with placebo. In controls serum IAPP increased in parallel with insulin (r=0.79), whereas in type 2 **diabetes** the increase in IAPP did not correlate with the increase in insulin. Thus, type 2 **diabetes** is assocd. with elevated circulating IAPP; **GLP-1** stimulates IAPP secretion both in healthy human subjects and in type 2 **diabetes**; IAPP secretion correlates with insulin secretion only in healthy subjects and no tin type 2 **diabetes**.
ST GLP1 insulin islet amyloid polypeptide **diabetes**
IT Non-insulin-dependent **diabetes** mellitus
(insulin and islet amyloid polypeptide were not correlated after stimulation with **glucagon-like peptide-1** in type 2 **diabetes**)
IT Blood glucose
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(insulin and islet amyloid polypeptide were not correlated after stimulation with **glucagon-like peptide-1** in type 2 **diabetes**)
IT 87805-34-3, Glucagon-related peptide I (human)
RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)
(insulin and islet amyloid polypeptide were not correlated after stimulation with **glucagon-like peptide-1** in type 2 **diabetes**)
IT 9004-10-8, Insulin, biological studies 106602-62-4, Islet amyloid polypeptide
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(insulin and islet amyloid polypeptide were not correlated after stimulation with **glucagon-like peptide-1** in type 2 **diabetes**)

L5 ANSWER 65 OF 126 CAPLUS COPYRIGHT 1999 ACS
AN 1997:718901 CAPLUS
DN 128:18885
TI **Glucagon-like peptide-1** (7-36)-amide confers glucose sensitivity to previously glucose-incompetent .beta.-cells in diabetic rats: in vivo and in vitro studies
AU Dachicourt, N.; Serradas, P.; Bailbe, D.; Kergoat, M.; Doare, L.; Portha, B.
CS Lab. Physiopathologie Nutrition, CNRS URA 307, Univ. Paris, Paris, 75 251, Fr.
SO J. Endocrinol. (1997), 155(2), 369-376
CODEN: JOENAK; ISSN: 0022-0795
PB Journal of Endocrinology
DT Journal
LA English
CC 2-6 (Mammalian Hormones)
AB The effects of **glucagon-like peptide-1**(7-36)-amide (**GLP-1**) on cAMP content and insulin release were studied in islets isolated from diabetic rats (n0-STZ model) which exhibited impaired glucose-induced insulin release. The authors first examd. the possibility of re-activating the insulin response to glucose in the .beta.-cells of the diabetic rats using **GLP-1** in vitro. In static incubation expts., **GLP-1** amplified cAMP accumulation (by 170%) and glucose-induced insulin release (by 140%) in the diabetic islets to the same extent as in control islets. Using a perifusion procedure, **GLP-1** amplified the insulin response to 16.7 mM glucose by diabetic islets and generated a clear biphasic pattern of insulin release. The incremental insulin response to glucose in the presence of **GLP-1**, although lower than corresponding control values (1.56 and 4.53 pg/min per ng islet DNA in diabetic and control islets resp.), became similar to that of control islets exposed to 16.7 mM glucose alone (1.09 pg/min per ng islet DNA). Since in vitro **GLP-1** was found to exert pos. effects on the glucose competence of the residual .beta.-cells in the n0-STZ model, the authors investigated the therapeutic effect of in vivo **GLP-1** administration on glucose tolerance and glucose-induced insulin release by n0-STZ rats. An infusion of **GLP-1** (10 ng/min pere kg; i.v.) in n0-STZ rats enhanced significantly basal plasma insulin levels, and, when combined with an i.v. glucose tolerance and insulin secretion test, it was found to improve glucose tolerance and the insulinogenic index, as compared with the resp. values of these parameters before **GLP-1** treatment.
ST glucagonlike peptide glucose pancreatic islet **diabetes**; insulin secretion glucose tolerance **diabetes** GLP1
IT Antidiabetic agents
Diabetes mellitus
(**GLP-1** confers glucose sensitivity to previously glucose-incompetent .beta.-cells in diabetic rats)
IT Blood glucose
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(**GLP-1** confers glucose sensitivity to previously glucose-incompetent .beta.-cells in diabetic rats)
IT Islet of Langerhans
(.beta.-cell; **GLP-1** confers glucose sensitivity to

previously glucose-incompetent .beta.-cells in diabetic rats)

IT 50-99-7, D-Glucose, biological studies
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BIOL (Biological study); PROC (Process)
(**GLP-1** confers glucose sensitivity to previously glucose-incompetent .beta.-cells in diabetic rats)

IT 118549-37-4, Insulinotropin
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**GLP-1** confers glucose sensitivity to previously glucose-incompetent .beta.-cells in diabetic rats)

IT 9004-10-8, Insulin, biological studies
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(**GLP-1** confers glucose sensitivity to previously glucose-incompetent .beta.-cells in diabetic rats)

IT 60-92-4, CAMP
RL: BPR (Biological process); MFM (Metabolic formation); BIOL (Biological study); FORM (Formation, nonpreparative); PROC (Process)
(**GLP-1** confers glucose sensitivity to previously glucose-incompetent .beta.-cells in diabetic rats)

L5 ANSWER 66 OF 126 CAPLUS COPYRIGHT 1999 ACS
AN 1997:687481 CAPLUS
DN 127:303498
TI **Glucagon-like peptide 1** and its potential in the treatment of non-insulin-dependent **diabetes** mellitus
AU Nauck, Michael A.; Holst, J. J.; Willms, B.
CS Med. Klin., Knappschaftskrankenhaus Bochum, Bochum, D-44892, Germany
SO Horm. Metab. Res. (1997), 29(9), 411-416
CODEN: HMMRA2; ISSN: 0018-5043
PB Thieme
DT Journal
LA English
CC 2-6 (Mammalian Hormones)
AB Studies examg. small groups of type 2-(NIDDM) diabetic patients have shown the potential of **glucagon-like peptide 1** (**GLP-1**) to normalize fasting hyperglycemia. Patient characteristics detg. the size of the effect have not been reported. Therefore, the results of four studies were analyzed. Exogenous **GLP-1** was administered i.v. or s.c. in 37 type 2-diabetic patients, age 60 yr; BMI 28.2 kg/m2; HbA1c 10.6 ; **diabetes** duration 10 yr, treatment with sulfonylureas, n =33, metformin, n =11, acarbose, n = 3. Results were analyzed using repeated measures anal. of variance and multiple regression anal. Exogenous **GLP-1** lowered fasting plasma glucose within 4-5 h from 12.8 to 5.3 mmol/L (placebo: 12.8 to 10.0). Only fasting glycemia and the route (i.v. vs. s.c.), but not gender, age, BMI, HbA1c, **diabetes** duration, treatment with sulfonylureas, metformin, or acarbose, were significant predictors of the plasma glucose concns. reached after the administration of **GLP-1** (variation: 3.4-8.5 mmol/L). In conclusion, **GLP-1** is able to normalize plasma glucose in all type 2-diabetic patients studied. This anal. underlines the great therapeutic potential of **GLP-1**.
ST glucagon related peptide NIDDM
IT Antidiabetic agents
Non-insulin-dependent **diabetes** mellitus
(**glucagon-like peptide 1** and its potential in the treatment of non-insulin-dependent **diabetes** mellitus)
IT Blood glucose
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(**glucagon-like peptide 1** and its potential in the treatment of non-insulin-dependent **diabetes** mellitus)
IT 89750-14-1, Glucagon-related peptide I
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**glucagon-like peptide 1** and its potential in the treatment of non-insulin-dependent **diabetes** mellitus)
IT 9004-10-8, Insulin, biological studies
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(**glucagon-like peptide 1** and its potential in the treatment of non-insulin-dependent **diabetes** mellitus)

L5 ANSWER 71 OF 126 CAPLUS COPYRIGHT 1999 ACS
AN 1997:540016 CAPLUS
DN 127:215285
TI Glucacon-like peptide 1 (**GLP-1**) as a new therapeutic approach for type 2-**diabetes**
AU Nauck, Michael A.; Holst, J. J.; Willms, B.; Schmiegel, W.
CS Dep. Medicine, Knappschafts-Krankenhaus, Bochum, D-44892, Germany
SO Exp. Clin. Endocrinol. Diabetes (1997), 105(4), 187-195
CODEN: ECEDFQ; ISSN: 0947-7349
PB Barth
DT Journal; General Review
LA English
CC 2-0 (Mammalian Hormones)
Section cross-reference(s): 14
AB A review with many refs. is given on **glucagon-like peptide 1** (**GLP-1**) as a new therapeutic approach for type 2-**diabetes**. **GLP-1** is a physiol. incretin hormone in normal humans explaining in part the augmented insulin response after oral vs. i.v. glucose administration. In addn., **GLP-1** also lowers glucagon concns., slows gastric emptying, stimulates (pro)insulin biosynthesis, reduces food intake upon intracerebroventricular administration in animals, and may enhance insulin sensitivity. Therefore, **GLP-1** opposes the type 2-diabetic phenotype characterized by disturbed glucose-induced insulin secretory capacity, hyperglucagonemia, moderate insulin deficiency, accelerated gastric emptying, overeating (obesity), and insulin resistance. The other incretin hormone, gastric inhibitory polypeptide (GIP), has lost almost all its activity in type 2-diabetic patients. In contrast, **GLP-1** glucose-dependently stimulates insulin secretion in diet- and sulfonylurea-treated type 2-diabetic patients and also in patients under insulin therapy long after sulfonylurea 2ndary failure. Exogenous administration of **GLP-1** ([7-37] or [7-36 amide]) in doses elevating plasma concns. to approx. 3-4 fold physiol. postprandial levels fully normalizes fasting hyperglycemia in type 2-diabetic patients. The half life of **GLP-1** is too short to maintain therapeutic blood plasma levels for sufficient periods by s.c. injections. Current research activities aim at finding **GLP-1** analogs with more suitable pharmacokinetic properties than the original peptide. Another approach could be the augmentation of endogenous release of **GLP-1**, which is abundant in L cells of the lower small intestine and the colon. Interference with sucrose digestion using .alpha.-glucosidase inhibition moves nutrients into distal parts of the gastrointestinal tract and, thereby, prolongs and augments **GLP-1** release. Enprostil, a prostaglandin E2 analog, fully suppresses GIP responses, while only marginally affecting insulin secretion and glucose tolerance after oral glucose, suggesting compensatory hypersecretion of addnl. insulinotropic peptides, possibly including **GLP-1**. Given the large amt. of **GLP-1** present in L cells, it appears worthwhile to look for more agents that could "mobilize" this endogenous pool of the "antidiabetogenic" gut hormone **GLP-1**.
ST review glucagon like peptide1 **diabetes**
IT Proteins (specific proteins and subclasses)
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(gene **glp-1; glucagon-like peptide 1** as a new therapeutic approach for type 2-**diabetes**)
IT Antidiabetic agents
Non-insulin-dependent **diabetes** mellitus
(**glucagon-like peptide 1** as a new therapeutic approach for type 2-**diabetes**)

L5 ANSWER 70 OF 126 CAPLUS COPYRIGHT 1999 ACS
AN 1997:542509 CAPLUS
DN 127:201022
TI **Glucagon-like peptide 1**-based protein heterologous expression in transformed mammal cell line, gene therapy of **diabetes**, and transformed cell line implants
IN Borts, Tracy L.; Broderick, Carol L.; Dimarchi, Richard D.; Grinnell, Brian W.; Miller, Anne R.
PA Eli Lilly and Co., USA; Borts, Tracy L.; Broderick, Carol L.; Dimarchi, Richard D.; Grinnell, Brian W.; Miller, Anne R.
SO PCT Int. Appl., 30 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM C12N005-00
ICS C12N015-00; C12N015-16; C12N015-09; A61K048-00
CC 3-2 (Biochemical Genetics)
Section cross-reference(s): 1, 2, 14
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 9729180	A1	19970814	WO 1997-US1978	19970206
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, YU, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
CA 2243718	AA	19970814	CA 1997-2243718	19970206
AU 9722631	A1	19970828	AU 1997-22631	19970206
EP 879279	A1	19981125	EP 1997-905834	19970206
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, PT, IE, FI, RO				

PRAI US 1996-12111 19960206
GB 1996-3847 19960223
WO 1997-US1978 19970206
OS MARPAT 127:201022
AB The invention provides a gene therapy method for delivering safe and effective, long-term amts. of **glucagon-like peptide 1 GLP-1**(7-37)-based proteins useful for treating Type I and Type II **diabetes**. The invention eliminates the need for s.c. injections and is able to provide tight glucose control. Plasmid vectors contg. **GLP-1** were constructed and pGT-h+tLB+**GLP-1**, pGT-h+tLB+Val8GLP-1, or pMT-h+tLB+Val8GLP-1 was transfected into human embryonic kidney cells. Monoclonal cell lines were screened for the ability to secrete **GLP-1**(7-37)-based protein into the culture medium. Transformed 293 cells were cultured then surgically transplanted under the kidney capsule of 8 wk old Zucker Diabetic Fatty male rats.
ST **glucagon like peptide 1**
diabetes therapy; gene therapy **GLP 1** peptide recombinant; implant recombinant cell **GLP 1**
diabetes
IT Metallothioneins
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(gene promoter, in vector; **glucagon-like peptide 1**-based protein heterologous expression in transformed mammal cell line, gene therapy of **diabetes**, and

transformed cell line implants)

IT 293 cell
Animal cell line
DNA sequences
Genetic vectors
Immunosuppressants
Immunotherapy
Insulin dependent **diabetes** mellitus
Mammal (Mammalia)
Non-insulin-dependent **diabetes** mellitus
Plasmid vectors
Protein secretion
Protein sequences
Transformation (genetic)
Transplant (organ)
(**glucagon-like peptide** 1-based protein heterologous expression in transformed mammal cell line, gene therapy of **diabetes**, and transformed cell line implants)

IT Promoter (genetic element)
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(in vector; **glucagon-like peptide** **1**-based protein heterologous expression in transformed mammal cell line, gene therapy of **diabetes**, and transformed cell line implants)

IT Plasmid vectors
(pGT-h+tLB+**GLP-1**; **glucagon-like peptide** **1**-based protein heterologous expression in transformed mammal cell line, gene therapy of **diabetes**, and transformed cell line implants)

IT Plasmid vectors
(pGT-h+tLB+Val8GLP-1; **glucagon-like peptide** **1**-based protein heterologous expression in transformed mammal cell line, gene therapy of **diabetes**, and transformed cell line implants)

IT Plasmid vectors
(pMT-h+tLB+Val8GLP-1; **glucagon-like peptide** **1**-based protein heterologous expression in transformed mammal cell line, gene therapy of **diabetes**, and transformed cell line implants)

IT Virus
(promoter, in vector; **glucagon-like peptide** **1**-based protein heterologous expression in transformed mammal cell line, gene therapy of **diabetes**, and transformed cell line implants)

IT 194551-05-8P
RL: BPN (Biosynthetic preparation); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(amino acid sequence; **glucagon-like peptide** **1**-based protein heterologous expression in transformed mammal cell line, gene therapy of **diabetes**, and transformed cell line implants)

IT 106612-94-6P, Rat GLP-I(7-37)
RL: BPN (Biosynthetic preparation); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(**glucagon-like peptide** **1**-based protein heterologous expression in transformed mammal cell line, gene therapy of **diabetes**, and transformed cell line implants)

IT 194616-47-2 194616-48-3
RL: BPR (Biological process); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(nucleotide sequence; **glucagon-like peptide** **1**-based protein heterologous expression in transformed mammal cell line, gene therapy of **diabetes**, and transformed cell line implants)

5 ANSWER 74 OF 126 CAPLUS COPYRIGHT 1999 ACS
AN 1997:466985 CAPLUS
DN 127:131311
TI **Glucagon-like peptide-1** (**GLP-1**): a trial of treatment in non-insulin-dependent **diabetes** mellitus
AU Todd, J. F.; Wilding, J. P. H.; Edwards, C. M. B.; Khan, F. A.; Ghatei, M. A.; Bloom, S. R.
CS Department of Metabolic Medicine, Royal Postgraduate Medical School, Hammersmith Hospital, London, W12 ONN, UK
SO Eur. J. Clin. Invest. (1997), 27(6), 533-536
CODEN: EJCIB8; ISSN: 0014-2972
PB Blackwell
DT Journal
LA English
CC 2-6 (Mammalian Hormones)
AB **Glucagon-like peptide-1** (7-36) amide (**GLP-1**) is released from the gut into the circulation after meals and is the most potent physiol. insulinotropic hormone in man. In contrast to presently available therapeutic agents for non-insulin-dependent **diabetes** mellitus (NIDDM), **GLP-1** has the advantages of both suppressing glucagon secretion and delaying gastric emptying. We report the first chronic study of s.c. (s/c) **GLP-1** treatment in NIDDM. Five patients with poorly controlled NIDDM were entered into a six-week, double-blind crossover trial. Each received three weeks treatment with s/c **GLP-1** 40 nmol or saline, given three times a day immediately before meals. A standardized test meal was given at the beginning and end of each treatment period. **GLP-1** reduced plasma glucose area under the curve (AUC) following the std. test meal by 25% (AUC, 0-180 mins, **GLP-1** start of treatment 482.2 .+-. 38.2 vs. saline start of treatment 635.7 .+-. 45.4 mmol min L-1, F = 16.4, P < 0.02). The beneficial effect of **GLP-1** on plasma glucose concn. was fully maintained for the three-week treatment period. Plasma glucagon levels were significantly lower for 60 min postprandially after **GLP-1** treatment. In this group of patients there was no significant increase in postprandial insulin levels with **GLP-1**. We have demonstrated a significant improvement in postprandial glycemic control with s/c **GLP-1** treatment that was fully maintained over a three-week treatment period. **GLP-1** improves glycemic control even in the absence of an insulinotropic effect and is a potential treatment for NIDDM.
ST glucagon like peptide **diabetes** mellitus; noninsulin dependent **diabetes** mellitus glucagon
IT Non-insulin-dependent **diabetes** mellitus
(trial of **glucagon-like peptide-1** (**GLP-1**) treatment in non-insulin-dependent **diabetes** mellitus)
IT 89750-14-1, Glucagon-related peptide I
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(trial of **glucagon-like peptide-1** (**GLP-1**) treatment in non-insulin-dependent **diabetes** mellitus)
IT 9007-92-5, Glucagon, biological studies
RL: BOC (Biological occurrence); BIOL (Biological study); OCCU (Occurrence)

L5 ANSWER 77 OF 126 CAPLUS COPYRIGHT 1999 ACS
AN 1997:438071 CAPLUS
DN 127:90598
TI In vivo regulation of human islet hormone secretion by **glucagon-like peptide-1**
AU D'alessio, David A.; Ensinck, John W.
CS Division of Endocrinology and Metabolism, Department of Medicine, University of Washington, Seattle, WA, USA
SO Front. Diabetes (1997), 13(Insulinotropic Gut Hormone Glucagon-Like Peptide-1), 132-141
CODEN: FDIADJ; ISSN: 0251-5342
PB Karger
DT Journal; General Review
LA English
CC 2-0 (Mammalian Hormones)
AB A review, with 35 refs., on the effects of **GLP-1** on insulin secretion, the effects of **GLP-1** on glucagon secretion, and the effects of **GLP-1** in persons with **diabetes** mellitus.
ST review pancreatic hormone secretion GLP1
IT Pancreatic hormones
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(human islet hormone secretion regulation by **glucagon-like peptide-1**)
IT 89750-14-1, Glucagon-related peptide I
RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)
(human islet hormone secretion regulation by **glucagon-like peptide-1**)

L5 ANSWER 82 OF 126 CAPLUS COPYRIGHT 1999 ACS
AN 1997:102919 CAPLUS
DN 126:181633
TI Effects of **glucagon-like peptide-1** on islet function and insulin sensitivity in noninsulin-dependent **diabetes** mellitus
AU Ahren, Bo; Larsson, Hillevi; Holst, Jens J.
CS Department of Medicine, Lund University, Malmo, Swed.
SO J. Clin. Endocrinol. Metab. (1997), 82(2), 473-478
CODEN: JCEMAZ; ISSN: 0021-972X
PB Endocrine Society
DT Journal
LA English
CC 2-6 (Mammalian Hormones)
AB Administration of the truncated **glucagon-like peptide 1** (**GLP-1**) has been considered for treatment of noninsulin-dependent **diabetes** mellitus (NIDDM). The authors studied its antidiabetogenic mechanism by examg. its influences on islet function and peripheral insulin sensitivity in six subjects (aged 56-74 yr) with well-controlled NIDDM. Islet function was evaluated with arginine stimulation at three plasma glucose levels (fasting, 14 mmol/L, and >28 mmol/L). **GLP-1** (1.5 pmol/kg per min i.v.) increased serum insulin levels at fasting glucose, at 14 mmol/L glucose, and at 28 mmol/L glucose (P = o.028). The acute insulin response (AIR) to 5 g i.v. arginine was increased by **GLP-1** at 14 mmol/L glucose, and the slopeAIR, i.e., the glucose potentiation of insulin secretion, was markedly increased by **GLP-1**. Plasma glucagon levels were reduced by **GLP-1**, and arginine-stimulated glucagon secretion (AGR) was inhibited by **GLP-1** at 14 and 28 mmol/L glucose. Glucose-induced inhibition of arginine-stimulated glucagon secretion (slopeAGR) was not significantly affected by **GLP-1**. In contrast, **GLP-1** did not affect the low insulin sensitivity during a hyperinsulinemic, euglycemic clamp. Thus, **GLP-1** improves islet dysfunction in **diabetes**, mainly by increasing the glucose-induced potentiation of insulin secretion. In contrast, the peptide does not seem to improve insulin resistance in NIDDM.
ST GLP1 islet function NIDDM
IT Islet of Langerhans
Non-insulin-dependent **diabetes** mellitus
(effects of **glucagon-like peptide-1** on islet function and insulin sensitivity in noninsulin-dependent **diabetes** mellitus)
IT 50-99-7, D-Glucose, biological studies
RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)
(effects of **glucagon-like peptide-1** on islet function and insulin sensitivity in noninsulin-dependent **diabetes** mellitus)
IT 9004-10-8, Insulin, biological studies 9007-92-5, Glucagon, biological studies
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(effects of **glucagon-like peptide-1** on islet function and insulin sensitivity in noninsulin-dependent **diabetes** mellitus)
IT 89750-14-1, Glucagon-related peptide I 107444-51-9, Human **glucagon-like peptide-1** (7-36) amide
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)

L5 ANSWER 85 OF 126 CAPLUS COPYRIGHT 1999 ACS
AN 1996:699523 CAPLUS
DN 126:29846
TI **GLP-1**(7-36) amide binding in liver membranes from streptozotocin diabetic rats
AU Valverde, I.; Delgado, E.; Merida, F.; Vicent, D.; Trapole, M. A.; Alcantara, A. J.; Vilanueva-Penocarrillo, M. I.
CS Dep. Metab. Nutr. Hormon., Fund. Jimenez Diaz, Madrid, E-28040, Spain
SO Diabetes, Nutr. Metab. (1996), 9(2), 103-105
CODEN: DNMEEW; ISSN: 0394-3402
PB Editrice Kurtis
DT Journal
LA English
CC 14-8 (Mammalian Pathological Biochemistry)
AB The binding of 125I-**GLP-1**(7-36) amide to liver plasma membranes from non-insulin and insulin-dependent diabetic (IDDM) rat models was compared with that from normal controls. Higher 125I-**GLP-1**(7-36) amide binding was found in streptozotocin-IDDM rats, apparently not accompanied by a change in the affinity, was indicative of an increase in the no. of 125I-**GLP-1**(7-36) amide liver binding sites, supporting the idea of a role of this peptide in hepatic glucose metab. and also an enhanced action on hepatic glucose removal in states of insulin deficiency.
ST glucagon like peptide receptor liver **diabetes**
IT Insulin-dependent **diabetes** mellitus
Liver
Non-insulin-dependent **diabetes** mellitus
(**GLP-1**(7-36) amide binding in liver membranes from streptozotocin diabetic rats)
IT **Glucagon-like peptide-1** receptors
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(**GLP-1**(7-36) amide binding in liver membranes from streptozotocin diabetic rats)
IT 118549-37-4, Glucagon-like peptide-I(7-36) amide
RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)
(**GLP-1**(7-36) amide binding in liver membranes from streptozotocin diabetic rats)

L5 ANSWER 88 OF 126 CAPLUS COPYRIGHT 1999 ACS
AN 1996:648895 CAPLUS
DN 125:318134
TI Normalization of insulin responses to glucose by overnight infusion of **glucagon-like peptide 1** (7-36) amide in patients with NIDDM
AU Rachman, Johathan; Gribble, Fiona M.; Barrow, Beryl A.; Levy, Jonathan C.; Buchanan, Keith D.; Turner, Robert C.
CS Diabetes Res. Lab., Radcliffe Infirmary, Oxford, 0X2 6HE, UK
SO Diabetes (1996), 45(11), 1524-1530
CODEN: DIAEAZ; ISSN: 0012-1797
DT Journal
LA English
CC 2-6 (Mammalian Hormones)
AB **Glucagon-like peptide 1** (**GLP-1**) is a natural enteric incretin hormone, which is a potent insulin secretagogue in vitro and in vivo in humans. Its effects on overnight glucose concns. and the specific phases of insulin response to glucose and non-glucose secretagogues in subjects with NIDDM are not known. The authors compared the effects of overnight i.v. infusion of **GLP-1** (7-36) amide with saline infusion, on overnight plasma concns. of glucose, insulin and glucagon in 8 subjects with NIDDM. The effects on basal (fasting) .beta.-cell function and insulin sensitivity were assessed using homeostasis model assessment (HOMA) and compared with seven age- and wt.-matched nondiabetic control subjects. The **GLP-1** infusion was continued, and the first- and second-phase insulin responses to a 2-h. 13 mM hyperglycemia clamp and the insulin response to a subsequent bolus of the non-glucose secretagogue, arginine, were measured. These were compared with similar measurements recorded after the overnight saline infusion and in the control subjects who were not receiving **GLP-1**. The effects on stimulated .beta.-cell function of lowering plasma glucose per se were assessed by a sep. overnight infusion of sol. insulin, the rate of which was adjusted to mimic the blood glucose profile achieved with **GLP-1**. Infusion of **GLP-1** resulted in significant lowering of overnight plasma glucose concns. compared with saline, with mean postabsorptive glucose concns. (2400-0800) of 5.6 and 7.8 mM, resp. Basal .beta.-cell function assessed by HOMA was improved from geometric mean 45% .beta. to 91% .beta. by **GLP-1**. First-phase incremental insulin response to glucose was improved by **GLP-1** from 8 pM to 116 pM, second-phase insulin response to glucose from 136 pM to 1156 pM and incremented insulin response to arginine from 443 pM to 811 pM. All responses on **GLP-1** were not significantly different from nondiabetic control subjects. Redn. of overnight glucose by exogenous insulin did not improve any of the phases of stimulate .beta.-cell functions. Prolonged i.v. infusion of **GLP-1** thus significantly lowered overnight glucose concns. in subjects with NIDDM and improved both basal and stimulated .beta.-cell function to nondiabetic levels. It may prove to be a useful agent in the redn. of hyperglycemia in NIDDM.
ST insulin glucose insulinotropin NIDDM
IT **Diabetes** mellitus
(maturity-onset, normalization of insulin responses to glucose by overnight infusion of **glucagon-like peptide 1** (7-36) amide in patients with NIDDM)
IT Pancreatic islet of Langerhans
(.beta.-cell, normalization of insulin responses to glucose by

overnight infusion of **glucagon-like peptide 1** (7-36) amide in patients with NIDDM)

IT 50-99-7, D-Glucose, biological studies 9004-10-8, Insulin, biological studies 9007-92-5, Glucagon, biological studies
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(normalization of insulin responses to glucose by overnight infusion of **glucagon-like peptide 1** (7-36) amide in patients with NIDDM)

IT 118549-37-4, Insulinotropin
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(normalization of insulin responses to glucose by overnight infusion of **glucagon-like peptide 1** (7-36) amide in patients with NIDDM)

L5 ANSWER 91 OF 126 CAPLUS COPYRIGHT 1999 ACS
AN 1996:630467 CAPLUS
DN 125:266590
TI Glucagon-like insulinotropic complexes, pharmaceutical compositions containing them and their use for treating **diabetes**
IN Galloway, John Allison; Hoffmann, James Arthur
PA Lilly, Eli, and Co., USA
SO Eur. Pat. Appl., 13 pp.
CODEN: EPXXDW
DT Patent
LA English
IC ICM C07K014-605
ICS A61K038-26; A61K047-02
CC 2-6 (Mammalian Hormones)
Section cross-reference(s): 1
FAN.CNT 3

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	EP 733644	A1	19960925	EP 1995-303423	19950523
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, NL, PT, SE				
	US 5705483	A	19980106	US 1995-407831	19950321
PRAI	US 1995-407831		19950321		
	US 1993-164277		19931209		

OS MARPAT 125:266590
AB The present invention provides novel complexes consisting of certain **glucagon-like peptide 1** (**GLP-1**) mols., R1XGluGlyThrSerAspValSerSerTyrLeuYGlyGlnAlaAlaLysZPhe IleAlaTrpLeuValLysGlyArgR2 (R1=L-His, D-His, desamino-His, etc.; X=Ala, Gly, Val, etc.; Y,Z=Glu, Gln, Ala, etc.; R2=NH2, Gly-OH; pI=6.0-9.0) assocd. with a divalent metal cation that is capable of copptg. with a **GLP-1** mol. Pharmaceutical compns. and methods of using such complexes for enhancing the expression of insulin in B-type islet cells is claimed, as is a method for treating maturity onset **diabetes** mellitus in mammals, particularly humans.
ST **glucagon like peptide 1** cation complex; **diabetes** therapeutic GLP1 cation complex
IT Antidiabetics and Hypoglycemics
(glucagon-like insulinotropic complexes, pharmaceutical compns. contg. them and use for treating **diabetes**)
IT Cations
(divalent, glucagon-like insulinotropic complexes, pharmaceutical compns. contg. them and use for treating **diabetes**)
IT 89750-14-1DP, Glucagon-related peptide I, Zn complex
RL: BPN (Biosynthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(analogs; glucagon-like insulinotropic complexes, pharmaceutical compns. contg. them and use for treating **diabetes**)
IT 7440-66-6, Zinc, biological studies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**glucagon-like peptide 1** complex; glucagon-like insulinotropic complexes, pharmaceutical compns.
contg. them and use for treating **diabetes**)

L5 ANSWER 94 OF 126 CAPLUS COPYRIGHT 1999 ACS
AN 1996:283392 CAPLUS
DN 124:333583
TI **Glucagon-like-peptide-1** (7-36) amide improves glucose sensitivity in beta-cells of NOD mice
AU Linn, T.; Schneider, K.; Goeke, B.; Federlin, K.
CS Centre of Internal Medicine, Justus Liebig University, Giessen, D-35385, Germany
SO Acta Diabetol. (1996), 33(1), 19-24
CODEN: ACDAEZ; ISSN: 0940-5429
DT Journal
LA English
CC 2-6 (Mammalian Hormones)
AB The effect of the insulinotropic gut hormone **glucagon-like-peptide-1** (**GLP-1**) was studied on the residual insulin capacity of prediabetic nonobese diabetic (NOD) mice, a model of insulin-dependent **diabetes** mellitus (type 1). This was done using isolated pancreas perfusion and dynamic islet perifusion. Prediabetes was defined by insulitis and fasting normoglycemia. Insulitis occurred in 100% of NOD mice beyond the age of 12 wk. K values in the i.v. glucose tolerance test were reduced in 20-wk-old NOD mice compared with age-matched non-**diabetes**-prone NOR (nonobese resistant) mice (2.4 vs. 3.8% min-1,). Prediabetic NOD pancreases were characterized by a complete loss of the glucose-induced first-phase insulin release. In perifused NOD islets **GLP-1**, at concns. already effective in normal islets, left the insulin release unaltered. However, a significant rise of glucose-dependent insulin secretion occurred for **GLP-1** concns. >0.1 nM. This was obtained with both techniques, dynamic islet perifusion and isolated pancreas perfusion, indicating a direct effect of **GLP-1** on the beta-cell. Anal. of glucose-insulin dose-response curves revealed a marked improvement of glucose sensitivity of the NOD endocrine pancreas in the presence of **GLP-1** (half-maximal insulin output without **GLP-1** 15.2 mM and with **GLP-1** 9.4 mM). It was concluded that **GLP-1** can successfully reverse the glucose-sensing defect of islets affected by insulitis.
ST glucagon like peptide glucose pancreas; **diabetes** glucose glucagon like peptide
IT Pancreatic islet of Langerhans
(**glucagon-like-peptide-1** (7-36) amide improves glucose sensitivity in beta-cells of nonobese diabetic mice)
IT **Diabetes** mellitus
(insulin-dependent, **glucagon-like-peptide-1** (7-36) amide improves glucose sensitivity in beta-cells of nonobese diabetic mice)
IT 50-99-7, D-Glucose, biological studies 118549-37-4, Insulinotropin
RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)
(**glucagon-like-peptide-1** (7-36) amide improves glucose sensitivity in beta-cells of nonobese diabetic mice)
IT 9004-10-8, Insulin, biological studies
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(**glucagon-like-peptide-1** (7-36) amide improves glucose sensitivity in beta-cells of nonobese diabetic mice)

L5 ANSWER 98 OF 126 CAPLUS COPYRIGHT 1999 ACS
AN 1996:140239 CAPLUS
DN 124:194441
TI **Glucagon-like peptide-1** and control of insulin secretion
AU Thorens, B.
CS Institute Pharmacology and Toxicology, Lausanne, CH-1005, Switz.
SO Diabete Metab. (1995), 21(5), 311-18
CODEN: DIMEDU; ISSN: 0338-1684
DT Journal; General Review
LA English
CC 2-0 (Mammalian Hormones)
AB A review, with 83 refs., on: the biol. actions of **GLP-1**; **GLP-1** receptor; cross-talk between glucose and **GLP-1** signaling pathways; role of **GLP-1**; GIP, and glucagon in the control of .beta.-cell cAMP levels; and GIP and non-insulin-dependent **diabetes**.
ST review insulin secretion GLP1
IT 89750-14-1, Glucagon-related peptide I
RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)
(**glucagon-like peptide-1** and control of insulin secretion)
IT 9004-10-8, Insulin, biological studies
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(**glucagon-like peptide-1** and control of insulin secretion)

L5 ANSWER 115 OF 126 CAPLUS COPYRIGHT 1999 ACS
AN 1994:290484 CAPLUS
DN 120:290484
TI **Glucagon-like peptide 1** enhances glucose tolerance both by stimulation of insulin release and by increasing insulin-independent glucose disposal
AU D'Alessio, David A.; Kahn, Steven E.; Leusner, Charles R.; Ensinck, John W.
CS Dep. Med., Univ. Washington, Seattle, WA, 98195, USA
SO J. Clin. Invest. (1994), 93(5), 2263-6
CODEN: JCINAO; ISSN: 0021-9738
DT Journal
LA English
CC 2-6 (Mammalian Hormones)
AB **Glucagon-like peptide 1** [7-36 amide] (**GLP-1**) has been shown to enhance insulin secretion in healthy and type II diabetic humans, and to increase glucose disposal in type I diabetic patients. To further define its action on glucose kinetics, the authors studied six healthy subjects who received either **GLP-1** (45 pmol/kg per h) or 150 mM saline on two mornings during which a modified i.v. glucose tolerance test was performed. Plasma insulin and glucose levels were analyzed using Bergman's minimal model of glucose kinetics to derive indexes of insulin sensitivity (SI) and glucose effectiveness at basal insulin (SG), the latter a measure of glucose disposition independent of changes in insulin.
In addn., basal insulin concns., the acute insulin response to glucose (AIRg), plasma glucagon levels, and the glucose disappearance const. (Kg) were measured on the days that subjects received **GLP-1** or saline. Compared with saline infusions, **GLP-1** increased the mean Kg from 1.61 to 2.65%/min. The enhanced glucose disappearance seen with **GLP-1** was in part the result of its insulinotropic effect, as indicated by a rise in AIRg from 240 to 400 pM. However, there was also an increase in SG from 1.77 to 2.65.times.10-2.cntdot.min-1, which was accounted for primarily by insulin-independent processes, viz glucose effectiveness in the absence of insulin. There was no significant effect of **GLP-1** on SI or basal insulin, and glucagon levels were not different during the glucose tolerance tests with or without **GLP-1**. Thus, **GLP-1** improves glucose tolerance both through its insulinotropic action and by increasing glucose effectiveness. These findings suggest that **GLP-1** has direct effects on tissues involved in glucose disposition. Furthermore, this peptide may be useful for studying the process of insulin-independent glucose disposal, and pharmacol. analogs may be beneficial for treating patients with **diabetes** mellitus.
ST glucagon peptide glucose tolerance insulin
IT 118549-37-4, **Glucagon-like peptide-1** (7-36)amide
RL: BIOL (Biological study)
(glucose tolerance improvement by, in humans, insulinotropic effect and glucose effectiveness enhancement in mechanism for)
IT 9004-10-8, Insulin, biological studies
RL: BIOL (Biological study)
(secretion of, in humans, **glucagon-like peptide 1** stimulation of, glucose tolerance

L5 ANSWER 119 OF 126 CAPLUS COPYRIGHT 1999 ACS
AN 1994:1033 CAPLUS
DN 120:1033
TI Effect of **glucagon-like peptide-1** (proglucagon 78-107 amide) on hepatic glucose production in healthy man
AU Hvidberg, Annemarie; Nielsen, Maibritt Toft; Hilsted, Jannik; Oerskov, Cathrine; Holst, Jens Juul
CS Dep. Endocrinol., Hvidovre Hosp., Copenhagen, DK-2200, Den.
SO Metab., Clin. Exp. (1994), 43(1), 104-8
CODEN: METAAJ; ISSN: 0026-0495
DT Journal
LA English
CC 2-6 (Mammalian Hormones)
AB The newly discovered intestinal hormone, **glucagon-like peptide-1** (**GLP-1**) (proglucagon 78-107 amide), stimulates insulin secretion and inhibits glucagon secretion in man and may therefore be anticipated to influence hepatic glucose prodn. To study this, the authors infused synthetic **GLP-1** sequentially at rates of 25 and 75 pmol.cntdot.kg-1.cntdot.h-1 into 8 healthy volunteers after an overnight fast and measured plasma concns. of glucose, insulin, and glucagon and glucose turnover by a technique involving infusion of 3-3H-glucose. Plasma levels of **GLP-1** increased by 21.3 and 75.4 pmol/L during the infusion, changes that were within physiol. limits. In a control expt. only saline was infused. During **GLP-1** infusion, plasma glucose level decreased significantly (from 5.3 to 4.7 and 4.3 pmol/L at the end of the two infusion periods). Despite this, plasma insulin level increased significantly (from 20.5 to a peak value of 33.5 pmol/L during the 2nd period), and plasma glucagon level decreased (from 9.3 to 7.1 pmol/L). Glucose rate of appearance (Ra) decreased significantly to 75% of the preinfusion values during **GLP-1** infusion. Glucose disappearance rate (Rd) did not change significantly, but glucose clearance increased significantly compared with saline. All parameters of glucose turnover remained const. during saline infusion. The authors conclude that **GLP-1** may potently control hepatic glucose prodn. and glucose clearance through its effects on the pancreatic glucoregulatory hormones. The effect of **GLP-1** on glucose prodn. is consistent with its proposed use in the treatment of type II **diabetes**.
ST glucose liver glucagonlike peptide 1
IT Blood sugar
(**glucagon-like peptide-1** effect on, in human)
IT Liver, metabolism
(glucose formation by, of human, **glucagon-like peptide-1** effect on)
IT 50-99-7, D-Glucose, biological studies
RL: FORM (Formation, nonpreparative)
(formation of, by liver of human, **glucagon-like peptide-1** effect on)
IT 107444-51-9
RL: BIOL (Biological study)
(glucose formation by liver and glucoregulatory hormone secretion response to, in human)
IT 9004-10-8, Insulin, biological studies 9007-92-5, Glucagon, biological studies
RL: BIOL (Biological study)
(secretion of, in human, **glucagon-like peptide-1** effect on)

L5 ANSWER 123 OF 126 CAPLUS COPYRIGHT 1999 ACS
AN 1993:94758 CAPLUS
DN 118:94758
TI Pancreatic beta-cells are rendered glucose-competent by the insulinotropic hormone **glucagon-like peptide-1** (7-37)
AU Holz, George G., IV; Kuhtreiber, Willem M.; Habener, Joel F.
CS Lab. MOl. Endocrinol., Massachusetts Gen. Hosp., Boston, MA, 02114, USA
SO Nature (London) (1993), 361(6410), 362-5
CODEN: NATUAS; ISSN: 0028-0836
DT Journal
LA English
CC 2-6 (Mammalian Hormones)
AB **Glucagon-like-peptide-1**(7-37) confers glucose sensitivity to glucose-resistant .beta.-cells, a phenomenon termed glucose competence. Induction of glucose competence by **GLP-1** resulst from its synergistic interaction with glucose to inhibit metabolically regulated potassium channels that are also targeted for inhibition by sulfonylurea drugs commonly used in the treatment of non-insulin-dependent **diabetes**. Glucose competence allows membrane depolarization, the generation of action potentials, and Ca2+ influx, events that are known to trigger insulin secretion.
ST insulinotropin glucose competence pancreas
IT Biological transport
(of calcium and potassium, in glucose resistance in pancreas .beta.-cells, insulinotropin effect on)
IT Electric activity
(depolarization, of pancreas .beta.-cells, in glucose competence induction by insulinotropin)
IT Electric activity
(potential, action, insulinotropin induction of, in pancreas .beta.-cells, glucose competence in relation to)
IT Pancreatic islet of Langerhans
(.beta.-cell, glucose resistance in, insulinotropin reversal of)
IT 7440-09-7, Potassium, biological studies
RL: BIOL (Biological study)
(channel-mediated transport of, in glucose resistance in pancreas .beta.-cells, insulinotropin effect on)
IT 89750-14-1, Glucagon-related peptide I
RL: BIOL (Biological study)
(glucose competence induction by, in pancreas .beta.-cells)
IT 7440-70-2, Calcium, biological studies
RL: BIOL (Biological study)
(influx of, in glucose competence induction by insulinotropin in pancreas .beta.-cells)
IT 56-65-5, 5'-ATP, biological studies
RL: BIOL (Biological study)
(potassium channels sensitive to, in glucose resistance in pancreas .beta.-cells, insulinotropin effect on)
IT 50-99-7, Glucose, biological studies
RL: BIOL (Biological study)
(resistance to, in pancreas .beta.-cells, insulinotropin reversal of)
IT 9004-10-8, Insulin, biological studies
RL: BIOL (Biological study)
(secretion of, in glucose resistance in pancreas .beta.-cells, insulinotropin effect on)

L5 ANSWER 125 OF 126 CAPLUS COPYRIGHT 1999 ACS
AN 1992:35159 CAPLUS
DN 116:35159
TI **Glucagon-like peptide-1** (**Glp-1**) analogs useful for **diabetes** treatment
IN Buckley, Douglas I.; Habener, Joel F.; Mallory, Joanne B.; Mojsov, Svetlana
PA USA
SO PCT Int. Appl., 50 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM C07K007-34
ICS C07K007-10; A61K037-02; A61K037-28
CC 2-6 (Mammalian Hormones)
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9111457	A1	19910808	WO 1991-US500	19910124
	W: CA, JP, US				
	RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LU, NL, SE				
	CA 2073856	AA	19910725	CA 1991-2073856	19910124
	EP 512042	A1	19921111	EP 1991-903738	19910124
	EP 512042	B1	19980408		
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE				
	JP 05506427	T2	19930922	JP 1991-503618	19910124
	AT 164852	E	19980415	AT 1991-903738	19910124
	ES 2113879	T3	19980516	ES 1991-903738	19910124
	US 5545618	A	19960813	US 1993-165516	19931210
PRAI	US 1990-468736	19900124			
	WO 1991-US500	19910124			
	US 1991-762768	19910920			

AB The invention provides effective analogs of the active **GLP-1** peptides, 7-34, 7-35, 7-36, and 7-37, which have improved characteristics for treatment of **diabetes** Type II. These analogs have amino acid substitutions at positions 7-10 and/or are truncated at the C-terminus and/or contain various other amino acid substitutions in the basic peptide. The analogs may either have an enhanced capacity to stimulate insulin prodn. as compared to glucagon or may exhibit enhanced stability in plasma as compared to **GLP-1** (7-37) or both. Either of these properties will enhance the potency of the analog as a therapeutic. Analogs having D-amino acid substitutions in the 7 and 8 positions and/or N-alkylated or N-acylated amino acids in the 7 position are particularly resistant to degrdn. in vivo. Activity and stability data for selected peptides are included.

ST glucagon like peptide analog **diabetes**

IT Antidiabetics and Hypoglycemics
(**glucagon-like peptide-1** analogs as, for type II **diabetes** treatment)

IT Peptides, biological studies
RL: BIOL (Biological study)
(**glucagon-like peptide-2** analogs, for type II **diabetes** treatment)

IT Molecular structure-biological activity relationship
(of **glucagon-like peptide-1** analogs, insulin stimulation and **diabetes** type II treatment in relation to)

IT Protein sequences
(of **glucagon-like peptide-2** analogs)

IT 106612-94-6 107444-51-9 119637-73-9 123475-27-4 123475-28-5
127650-06-0 138324-89-7 138324-90-0 138324-91-1 138324-92-2
138324-93-3 138324-94-4 138324-95-5 138324-96-6 138324-97-7
138324-98-8 138324-99-9 138325-00-5 138347-75-8 138347-76-9
RL: BIOL (Biological study)
(for **diabetes** type II treatment)

IT 138347-77-0
RL: BIOL (Biological study)
(**glucagon-like peptide-1**
analogs stability in relation to)

IT 138325-01-6
RL: BIOL (Biological study)
(insulin-stimulating activity of, **diabetes** type II treatment
in relation to)

IT 9004-10-8, Insulin, biological studies
RL: BIOL (Biological study)
(stimulation of, **glucagon-like peptide-**
1 analogs for, for **diabetes** type II treatment)

L15 ANSWER 1 OF 3 MEDLINE
ACCESSION NUMBER: 95342389 MEDLINE
DOCUMENT NUMBER: 95342389 PubMed ID: 7617173
TITLE: A novel mode of immunoprotection of neural xenotransplants: masking of donor major histocompatibility complex class I enhances transplant survival in the central nervous system.
COMMENT: Erratum in: Neuroscience 1995 Jun;66(3):761
AUTHOR: Pakzaban P; Deacon T W; Burns L H; Dinsmore J; Isacson O
CORPORATE SOURCE: Neurogeneration Laboratory, McLean Hospital, Belmont, MA 02178, USA.
CONTRACT NUMBER: 5T32 NS07340 (NINDS)
NS29178 (NINDS)
NS30064 (NINDS)
+
SOURCE: NEUROSCIENCE, (1995 Apr) 65 (4) 983-96.
Journal code: 7605074. ISSN: 0306-4522.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199508
ENTRY DATE: Entered STN: 19950905
Last Updated on STN: 19970203
Entered Medline: 19950822

AB To determine the role of major histocompatibility complex (MHC) class I in **immunological** rejection of neural xenotransplants, F(ab')2 fragments of a monoclonal antibody to porcine MHC class I were used to **mask** this complex on porcine fetal striatal cells transplanted into rat striata previously lesioned with quinolinic acid. Presence of MHC class I on the surface of porcine striatal cells was confirmed by fluorescence-activated cell sorting prior to F(ab')2 treatment. At three to four months post-transplantation, survival of F(ab')2-treated xenografts was assessed by means of donor-specific immunostaining and compared to that of untreated xenografts in non-immunosuppressed rats and in rats immunosuppressed with cyclosporine A. In this study, **masking** of donor MHC class I by F(ab')2 treatment resulted in enhanced xenografts survival compared to the non-immunosuppressed controls (graft survival rates, 52% and 7%, respectively; $P < 0.005$) at survival times up to four months. While xenograft survival in F(ab')2-treated animals was not significantly different from that in cyclosporine-treated rats (74% graft survival), mean graft volume in F(ab')2-treated animals was smaller than that in cyclosporine-treated animals (1.07 +/- 0.30 mm3 versus 3.14 +/- 0.51 mm3; $P < 0.005$). The cytoarchitectonic organization of the xenografts was similar in F(ab')2- and cyclosporine-treated animals, and grafts in both groups exhibited long distance target-directed axonal outgrowth. The pattern of immunoreactivity to porcine MHC class I in the xenografts corresponded to the regional distribution of donor glia. In xenografts undergoing rejection, infiltration with host inflammatory cells was restricted to necrotic graft remnants and spared the nearby host structures. We conclude that MHC class-I-restricted immune mechanisms play an important role in neural xenograft rejection and that **masking** of this complex on donor cells may provide a useful strategy for immunoprotection of neural xenografts.

Last Updated on STN: 19980206
Entered Medline: 19881011

AB High-performance liquid chromatography-purified 125I-vasoactive intestinal peptide (VIP) bound to T-47D human breast cancer cells in a specific, saturable, and reversible manner. Scatchard plots were compatible with the presence of one class of VIP receptors with high affinity (Kd = 4.5 X 10(-10) M VIP, and Bmax = **293** fmol/mg protein). The neuropeptide and its natural analogues inhibited the binding of 125I-VIP and stimulated cyclic AMP (cAMP) generation in T-47D cells 96-fold (EC50 = 7 X 10(-10) M VIP), in the following order of potency: VIP greater than helodermin greater than human peptide with N-terminal histidine and C-terminal methionine greater than human pancreatic growth hormone-releasing factor greater than human secretin. In contrast, 125I-VIP binding was not displaced by pancreatic glucagon, human oxyntomodulin, truncated **glucagon-like peptide-1**, glucagon-like peptide-2, the somatostatin analogue SMS 201-995, gastric inhibitory peptide, and a series of steroid hormones or peptides unrelated to VIP. VIP also increased cAMP generation in seven other human breast cancer cell lines: H4-66B, HSL 53, HSL 78, MCF 7, MDA-MB231, T-47D2, and ZR75-1. Adenylate cyclase activity rose from 72.2 +/- 14 to 1069 +/- 66 pmol cAMP/min mg protein after the addition of 10(-7) M VIP to T-47D plasma membranes. In agreement with our pharmacological results and the Scatchard analysis of the binding data, sodium dodecyl sulfate-polyacrylamide gel electrophoresis of the solubilized receptor in the T-47D membranes permitted identification of one autoradiographic band with a molecular weight of 69,000. The sensitivity of the Mr 69,000 binding site to GTP and low doses of VIP implies that in T-47D cells, this component constitutes the membrane domain involved in the functional regulation of adenylate cyclase by VIP receptors. Our results indicate a role for the VIP receptor-cAMP system in human breast cancer cells.

OTHER SOURCE: GENBANK-AF047715; GENBANK-AF047716
ENTRY MONTH: 199806
ENTRY DATE: Entered STN: 19980708
Last Updated on STN: 20000303
Entered Medline: 19980624

AB Compartmentalization of protein kinases with substrates is a mechanism that may promote specificity of intracellular phosphorylation events. We have cloned a low-molecular weight A-kinase Anchoring Protein, called AKAP18, which targets the cAMP-dependent protein kinase (PKA) to the plasma membrane, and permits functional coupling to the L-type calcium channel. Membrane anchoring is mediated by the first 10 amino acids of AKAP18, and involves residues Gly1, Cys4 and Cys5 which are lipid-modified through myristoylation and dual palmitoylation, respectively. Transient transfection of AKAP18 into HEK-**293** cells expressing the cardiac L-type Ca2+ channel promoted a 34 9% increase in cAMP-responsive Ca2+ currents. In contrast, a targeting-deficient mutant of AKAP18 had no effect on Ca2+ currents in response to the application of a cAMP analog. Further studies demonstrate that AKAP18 facilitates **GLP-1**-mediated insulin secretion in a pancreatic beta cell line (RINm5F), suggesting that membrane anchoring of the kinase participates in physiologically relevant cAMP-responsive events that may involve ion channel activation.

L3 ANSWER 7 OF 9 MEDLINE
ACCESSION NUMBER: 1998006423 MEDLINE
DOCUMENT NUMBER: 98006423 PubMed ID: 9348200
TITLE: Studies of melatonin effects on epithelia using the human embryonic kidney-293 (HEK-293) cell line.
AUTHOR: Chan C W; Song Y; Ailenberg M; Wheeler M; Pang S F; Brown G M; Silverman M
CORPORATE SOURCE: The Clarke Institute of Psychiatry, Toronto, Ontario, Canada.
SOURCE: ENDOCRINOLOGY, (1997 Nov) 138 (11) 4732-9.
Journal code: 0375040. ISSN: 0013-7227.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199711
ENTRY DATE: Entered STN: 19971224
Last Updated on STN: 19971224
Entered Medline: 19971124

AB The expression of melatonin receptors (MR) of the Mel1a subtype in basolateral membrane of guinea pig kidney proximal tubule suggests that melatonin plays a role in regulating epithelial functions. To investigate the cellular basis of melatonin action on epithelia, we sought to establish an appropriate in vitro culture model. Epithelial cell lines originating from kidneys of dog (MDCK), pig (LLC-PK1), opossum (OK), and human embryo (HEK-**293**) were each tested for the presence of MR using 2-[125I]iodomelatonin (125I-MEL) as a radioligand. The HEK-**293** cell line exhibited the highest specific 125I-MEL binding. By intermediate filament characterization, the HEK-**293** cells were determined to be of epithelial origin. Binding of 125I-MEL in HEK-**293** cells demonstrated saturability, reversibility, and high specificity with an equilibrium dissociation constant (Kd) value of 23.8 +/- 0.5 pM and a maximum number of binding sites (Bmax) value of 1.17 +/- 0.11 fmol/mg protein (n = 5), which are comparable with the reported Kd and Bmax values in human kidney cortex. Coincubation with GTPgammaS (10 microM) and pertussis toxin (100 ng/ml) provoked a marked decrease in binding affinity (Kd was increased by a factor of 1.5-2.0), with no significant difference in Bmax. Melatonin (1 microM) decreased the forskolin (10 microM) stimulated cAMP level by 50%. HEK-**293** cells do not express dopamine D1A receptor. Following transient transfection of HEK-**293** cells with human dopamine D1A receptor (hD1A-R), exposure of the cells to dopamine stimulated an increase in the level of cAMP. Similarly, transient transfection of HEK-**293** cells with rat **glucagon-like peptide-1** (**GLP-1**), glucose-dependent insulinotropic peptide (GIP), and PTH type 1 receptors, each resulted in an hormone inducible increase in cAMP levels. Surprisingly, only the stimulatory

effect of dopamine could be inhibited by exposure to melatonin. The inhibitory effect of melatonin on dopamine D1-induced increase in cAMP was completely inhibited by pertussis toxin (100 ng/ml, 18 h). Immunoblot and immunocytochemical studies were carried out using two polyclonal antibodies raised against the extra and cytoplasmic domains of Mel1a receptor. Immunoblot studies using antibody against the cytoplasmic domain of Mel1a receptor confirmed the presence of a peptide blockable 37 kDa band in HEK-**293** cells. Indirect immunofluorescent studies with both antibodies revealed staining predominantly at the cell surface, but staining with the antibody directed against the cytoplasmic domain required prior cell permeabilization. By RT-PCR, HEK-**293** cells express both Mel1a and Mel1b messenger RNAs, but the messenger RNA level for Mel1b is several orders of magnitude lower than for Mel1a. We conclude that HEK-**293** cells express MR predominantly of the Mel1a subtype. Our evidence suggests that one of the ways that melatonin exerts its biological function is through modulation of cellular dopaminergic responses.

L3 ANSWER 8 OF 9 MEDLINE
ACCESSION NUMBER: 96026438 MEDLINE
DOCUMENT NUMBER: 96026438 PubMed ID: 7589461
TITLE: Stimulation of cloned human **glucagon-like peptide 1** receptor expressed in HEK **293** cells induces cAMP-dependent activation of calcium-induced calcium release.
COMMENT: Erratum in: FEBS Lett 1996 Mar 4;381(3):262
AUTHOR: Gromada J; Rorsman P; Dissing S; Wulff B S
CORPORATE SOURCE: Novo Nordisk A/S, Copenhagen, Denmark.
SOURCE: FEBS LETTERS, (1995 Oct 9) 373 (2) 182-6.
Journal code: 0155157. ISSN: 0014-5793.
PUB. COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199511
ENTRY DATE: Entered STN: 19960124
Last Updated on STN: 19980206
Entered Medline: 19951130

AB The actions of **glucagon-like peptide-1**(7-36)amide (**GLP**-1(7-36)amide) on cellular signalling were studied in human embryonal kidney **293** (HEK **293**) cells stably transfected with the cloned human **GLP-1** receptor. The cloned **GLP-1** receptor showed a single high-affinity binding site (Kd = 0.76 nM). Binding of **GLP-1**(7-36)amide stimulated cAMP production in a dose-dependent manner (EC50 = 0.015 nM) and caused an increase in the intracellular free Ca2+ concentration ([Ca2+]i). The latter effect reflected Ca(2+)-induced Ca2+ release and was suppressed by ryanodine. We propose that the ability of **GLP-1**(7-36)amide to increase [Ca2+]i results from sensitization of the ryanodine receptors by a protein kinase A dependent mechanism.

L3 ANSWER 9 OF 9 MEDLINE
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